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The Effects of Polypharmacy on Liver Disease and Kidney Dysfunction in Older Adults

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Abstract

The Effects of Polypharmacy on Liver Disease and Kidney Dysfunction in Older Adults

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Polypharmacy, prevalent among older adults, is known to increase the risks of falls and delirium. It could also damage the liver and kidney by burdening the function of drug metabolism and excretion. While many studies have identified the specific drugs that adversely affect the function, it raises questions about whether the polypharmacy whose subset contains individual drugs adds to the effect. Thus, this dissertation aimed to determine whether polypharmacy adversely affects the function. Specific aims were (1) to determine the temporal association between kidney dysfunction and polypharmacy controlling risk factors, (2) to determine the roles of hepatotoxic drug exposures as moderator and/or mediator on the association between polypharmacy and liver disease.

As a nested case control study, the National Health Insurance Service-Senior Cohort data were used to identify the case of kidney dysfunction based on a defined decline in eGFR over two health-checkup periods, and the liver disease case based on an initial visit with a primary diagnosis code of liver diseases (K70, K71, K73-K76). Polypharmacy was measured based on daily counts of active ingredients for 1-year prior to the case identification and classified into N-PP (less than five), PP (five to less than 10), and E-PP (10 or more). Conditional logistic regression was used for matched pairs of cases and controls.

Polypharmacy was significantly associated with the increase in the risk of kidney dysfunction even after adjusting other risk factors (PP: aOR= 1.21, 95% CI= 1.14 - 1.29; E-PP: aOR = 1.46, 95% CI= 1.30 - 1.64). There was also significant association with polypharmacy even after considering hepatotoxic drugs as moderator and/or mediator (Total Effect: aOR=1.06, 95% CI=1.03-1.08) in liver disease, which was mainly mediated by hepatotoxic drugs.

These findings inform healthcare providers and policy makers of the importance of polypharmacy management, especially among older adults with kidney dysfunction.

Keywords: Polypharmacy, Liver Disease, Kidney Dysfunction, Older adults

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I. Introduction

1. Polypharmacy

Polypharmacy, defined as the concurrent use of multiple medicines, causes drug-drug interactions and alters the pharmacokinetics for each drug, and thus, it risks adverse drug reactions [1-3]. While the issue of polypharmacy has been around for quite some time, its prevalence has rapidly increased over time [4-6] and it remains a public health problem [3,7,8].

It is quite prevalent not only in Korea [9-11] but also in other countries [5,6,12], especially among older adults. Polypharmacy is more common among older adults [2,13,14] because older people tend to have more multi-morbidity. In Korea, it was revealed that the elderly has higher exposure to polypharmacy with 44.1% and 9.5% comparing to the average with 19.9% and 1.7%, respectively from month-based and year-based analysis [15].

Besides, the renal and hepatic function decreases with aging. Older adults, thus, are at a greater risk of polypharmacy such as adverse drug reactions and other harms to health not only from the higher exposure to polypharmacy but also from their weakening physiological functions [7,16-20].

2. Definition of Polypharmacy

Polypharmacy means that a patient takes many medications at the same time. It is based on the Greek etymol ogy of "poly" which means two or more and "pharmakon" meaning medicine [21]. Previous studies on polypharmacy have no consensus on a definition. The WHO (2004) defines it to as, *"the administration of many drugs at the same time or the administration of an excessive number of drugs"* [22], however, there is no precise definition of how many drugs constitute it.

Polypharmacy, in general, has been defined in two ways: first, simply by the number of drugs and second, by clinical criteria, whether or not there is an inappropriate prescriptions [23]. The latter is based on pre-defined criteria, such as Beers criteria or STOPP / START*, which is closer to detecting inappropriate medications rather than the decision of polypharmacy—the use of multiple drugs. The former definition is most commonly used. It is supported by the systematic review of recently published definitions of polypharmacy [8]. Although the numerical definition is a simple way of defining polypharmacy, there should also be many considerations, such as: (Refer to Figure 1)

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* Screening Tool of Older Persons' potentially inappropriate Prescriptions/Screening Tool to Alert to Right Treatment

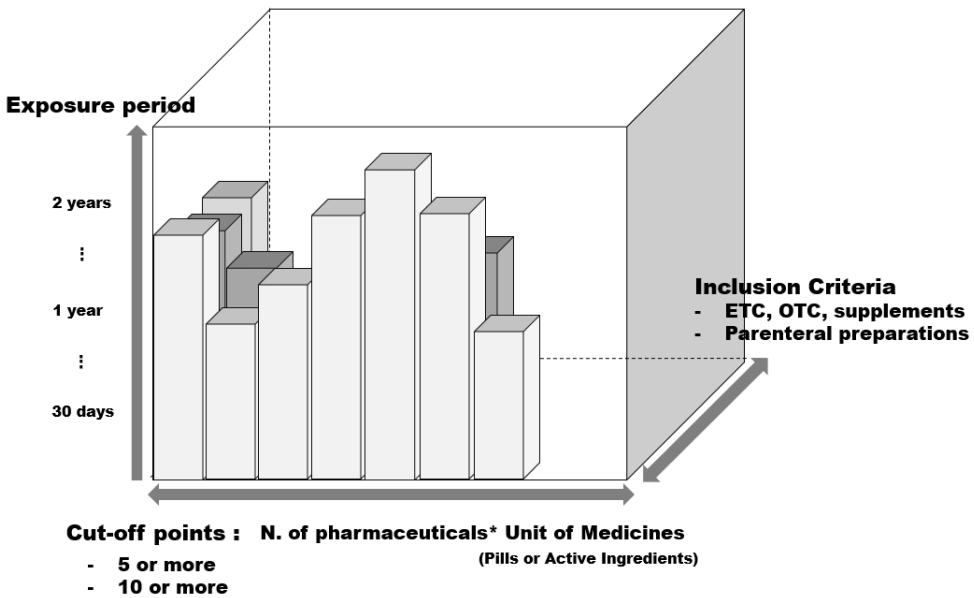

Figure 1. Dimension for Polypharmacy Definition

■ Cut-off point

- The numerical definitions of polypharmacy vary from study to study. Polypharmacy had been defined as long-term use of two or more drugs [1,2], or average daily doses of three or more [24], and five or more [25]. The most commonly reported definition was found to be at least five daily averages [8], in addition, within a study, more than ten multi-drugs called excessive polypharmacy and/or hyper-polypharmacy were used.

■ Exposure periods

- It is also essential to define the period of exposure to multiple drug-use to define polypharmacy. However, there is no standard for this. Different exposure periods have been applied in various studies. Polypharmacy was defined as long-term use of two or more drugs for 480 days or more [1,2], and some recent studies have defined exposure periods of two years [26]. Additionally, in a study, varying exposure periods were used including thirty days, one year, and two years. According to these criteria, the prevalence of polypharmacy can vary widely.

■ Inclusion Criteria

- According to the studies and data sources, the range of medicines included counting for the number of drugs could be different. For example, a survey of patients and their caregivers will answer the question "how many medications do you take recently?" If possible, they can bring the medication they take or their EMR may be linked. In this case, the drugs included are over the counter drugs, supplements, in addition to prescription drugs. In contrast, in large population data using health claims data, only the prescription drug covered are

included. On top of that, the criteria for including other parenteral preparations such as eye drops, dermal patches and ointments might vary from study to study.

■ Unit of Medication

- There are various criteria for whether to merely classify the pills or to the ingredients while calculating the number of drugs. While some studies simply counted the number of pills because of restricted information especially from questionnaires, many studies have counted the ingredients to consider the actual difference in numbers in fixed dose combination drugs. In this case, however, complexity should be simplified especially in digestives or herbal extracts using the ATC code. Additionally, there is a difference between the overdose or normal dose despite using one pharmaceutical, which could be addressed by adopting the concept of the daily drug dose.

3. Clinical Consequences from Polypharmacy

Many studies have examined the negative effect of polypharmacy on various health outcomes such as falls [27-30], fractures [31], delirium [32], dementia [10,33], and Parkinsonism [34] among older adults. However, these outcomes might be caused by improperly taking certain drugs like anticholinergic drugs or benzodiazepines rather than polypharmacy itself. Unfortunately, little effort has been made to distinguish risk from polypharmacy by investigating its association with the organs where drugs are metabolized and excreted.

(1) The Effects of Polypharmacy on Kidney Dysfunction

Polypharmacy could seriously damage the kidneys because it burdens them to excrete a wide range of drugs and their m etabolites [20,35]. Few studies have investigated the association between polypharmacy and kidney function. Among those, two examined the risk of acute renal failure [36,37] and two others examined chronic kidney diseases (CKD) [38,39]. However, the two studies on CKD reported inconsistent results because they used different approaches for risk adjustment and different operational definitions of CKD. Furthermore, the study results were susceptible to bias from cross-sectional data.

Therefore, there is a critical need to generate more scientific evidence about the temporal association between polypharmacy and risk of kidney dysfunction.

(2) The Effects of Polypharmacy on Liver Disease

There are various risk factors for liver disease, depending on their types, such as alcohol, exposure to hepatotoxin, hepatitis virus and medications. Because polypharmacy consists of multiple medicines, it would be a drug induced liver injury, DILI that can be used as a health outcome predicted by polypharmacy. However, there are some considerations in only using DILI as a health outcome from polypharmacy. First, the recorded diagnosis codes may be less precise in that the most common codes used are ‘non-specified’. These diseases, known as Non-Alcoholic Liver Diseases, are what could have not been explained by specific causes like toxins, alcohols, and drugs. In other words, the causes had not been identified and they might be polypharmacy or something else. Therefore, it is reasonable to study the potential risk of polypharmacy among these liver diseases.

The paradigm of studying the relation between drugs and liver disease is focused on identifying a causative agent from multiple drugs [40,41]. However, most drugs can cause liver injuries

[41-43] because many of them are metabolized in the liver and, thus, pose a potential risk of hepatotoxicity [42]. Considering that the liver is the centre of metabolism, it is critical not only to identify a causative agent but also to examine polypharmacy itself as a potential cause of liver disease [42,44-46].

The impacts of polypharmacy on the liver, however, have not been studied which is already known as the organ of metabolizing all the pharmaceutical drugs. Therefore, it is crucial to examine polypharmacy as a potential cause of liver disease besides other medicines that are known as hepatotoxicity drugs.

4. Strategies for Reducing Polypharmacy

Polypharmacy can adversely affect individuals' health and finally lead to public health problems with its increasing prevalence. Not only will the health outcomes deteriorate but also the health care finances. This is because medical expenses will be wasted on unnecessary and inappropriate medicines and further treatment will be required to address its adverse health outcomes.

There have been trials to assess the size and/or severity of the problem and to reduce it [47-51]. While there were still a lack of systemic strategies and/or policies to manage polypharmacy, its core elements were: detecting inappropriate medicines; and reducing the unnecessary and ineffective prescribing, so called deprescribing.

(1) Criteria for detecting inappropriate medicines

There are several tools for detecting inappropriate prescriptions. They are generally categorized as explicit-based and implicit-based tools [48,50]. Explicit tools provide lists of drugs to be avoided, especially among the elderly population and the most widely used are the Beers criteria and the STOPP/START

[48,50]. Contrary to the explicit tools which were settled and fixed in advance, the implicit tools are real time jobs and require clinical judgement for interpretation [48,50]. By nature, these approaches are focused on individual patients but depend on the individual clinician' s opinion [48,50].

(2) Deprescribing

Though the approaches are different, both ultimately aim to remove inappropriate medicines and reduce the number of d rugs and burden for patients. It is known as deprescribing where the drug dosage is decreased and eventually discontinuing them under the supervision of health care professionals[47,51]. To minimize the concerns about entirely relying on the judgement of an expert, the evidence-based guidelines were established to support healthcare providers in deprescribing [50,51].

Adoption of polypharmacy management [47] is encouraged due to the increased awareness about the importance of deprescribing. Several studies have shown that it is a promising approach to eliminate unnecessary and inappropriate medication and further reduce mortality and improve quality of life[50,51]. However, it has not been mentioned well and neither has it been suitably applied in the Korean health care setting.

II. Objective

The purpose of this dissertation was to understand polypharmacy and its clinical consequences on the kidneys and liver among older Korean patients using two studies and to suggests polypharmacy management.

(1) The Effects of Polypharmacy on Kidney Dysfunction

This study aimed to document the temporal relationship between polypharmacy and kidney dysfunction, and further, to determine the significant association after adjusting disease- and medication-specific, and lifestyle-related risk factors.

(2) The Effects of Polypharmacy on Liver Disease

This study also aimed to examine the association between polypharmacy and liver disease considering the exposure to hepatotoxic drugs as moderator and/or mediator.

- The effect of polypharmacy on liver disease would be different depending on the exposure to hepatotoxic drugs.
- The more the exposure to polypharmacy, the more the exposure to hepatotoxic drugs and more the likelihood to have liver disease.

III. Methods

1. Data

The data used in this study are the National Health Insurance Service—Senior Cohort (NHIS-SC), a population-based cohort established by the National Health Insurance Service, which is a single-payer in South Korea. It was developed in 2002 by randomly selecting a representative sample of 558,147 seniors, comprising about 10% of the total eligible population aged 60 or more (5,5000,000 persons)., and it was followed for 11 years—unless the participant was disqualified due to death or emigration—until 2013. The NHIS-SC contains information on insurance membership, income level, health insurance claims, and lab values from mandatory periodic health check-ups for selected populations. During the health check-ups, information on lifestyles was collected through interviews.

Consequently, two studies of this dissertation were approved respectively by the Seoul National University Institutional Review Board (IRB No. E1801/001-001; IRB No. E1801/001-002). Additionally, obtaining informed consent was waived because these studies analyze the secondary data collected from claims. All methods were performed in accordance with the approved protocol.

2. Study Design and Patients

Both studies were conducted as nested case control studies. Using the NHIS-SC, each cohort was set up as the older patients who had undergone at least one of health care utilization. Cases were defined appropriately according to each study aims, controls were selected among them without defining the case during the study period, and were matched up to the cases based on age, gender, region, income, and coverage type using greedy algorithm. Details of each study design are as follows.

(1) The Effects of Polypharmacy on Kidney Dysfunction

In this study, the NHIS-SC data from 2009 to 2013 were used since the key variable of serum creatinine (SCr), an indica tor of kidney function, became available in 2009. Patients aged 65-84 who had a normal range of serum creatinine (SCr of 0.5-1.5) and a normal value of estimated Glomerular filtration rate (eGFR of 60 or higher) at a baseline health check-up were included. The oldest age group (85 or older) was excluded because they are known to be quite different from the other groups. Furthermore, patients who had not had their next health check-up within three years from the baseline date (n=87,147) were excluded. Patients with outlier values of SCr at the last

check-up as well as those with a history of renal disease prior to the case's event date were excluded.

Kidney dysfunction was defined as a follow-up eGFR lower than 60 with a decline rate of 10% or more from the initial eGFR. Controls were those patients without renal disease diagnoses who had normal eGFR at initial and follow-up check-ups. After excluding patients without health check-up information, cases (n=14,657) and controls (n=67,278) were matched 1:1 based on a wide range of covariates, excluding risk factors. The matching was exact in the year of baseline examination, gender, age, chronic kidney disease stage at the baseline and follow-up duration except the nearest neighbor in resident area, medical insurance coverage, and income level. After matching, the numbers of the final sample were 14,577 each for case and control group. (Refer to Figure 2)

(2) The Effects of Polypharmacy on Liver Disease

The cohort was set up to provide the patients with at least one healthcare service. It had no record of any liver related diseases (viral hepatitis, hemochromatosis, jaundice NOS, Reye's syndrome, and Wilson's disease), liver cancer, metastatic cancer, or AIDS.

Cases were defined as the new liver disease diagnosed at

least once from 2007 to 2013. The new patients were regarded as those without previous diagnosis of liver disease for 5 years. While it is hard to say it is liver disease from a single diagnosis; having a single diagnosis of liver disease does not necessary mean that this is not a liver disease. It means that the patients have a suspected liver abnormality. This is regarded as pre-disease state for liver disease and should be distinguished from people with a normal state of liver. Cases of liver disease excluded liver disease in disease classified elsewhere and severe status of hepatic failure, which might be difficult to be resulted from polypharmacy, while toxic liver disease, alcoholic liver disease and non-alcoholic liver disease to examine whether there would be synergistic effect of polypharmacy apart from toxins and/or alcohol. Therefore, the broad range of liver diseases were used to examine the potential effect of polypharmacy, and analyzed according to specific types using sub-group analysis.

Control groups were matched with a 1:1 ratio to each case by age, gender, region, income, and coverage type. Patients without health examination data were excluded from the selected cases and control groups. The final study population with health check-up information which were used for risk adjustment, were 26,623 each for case and control group (Refer to Figure 3).

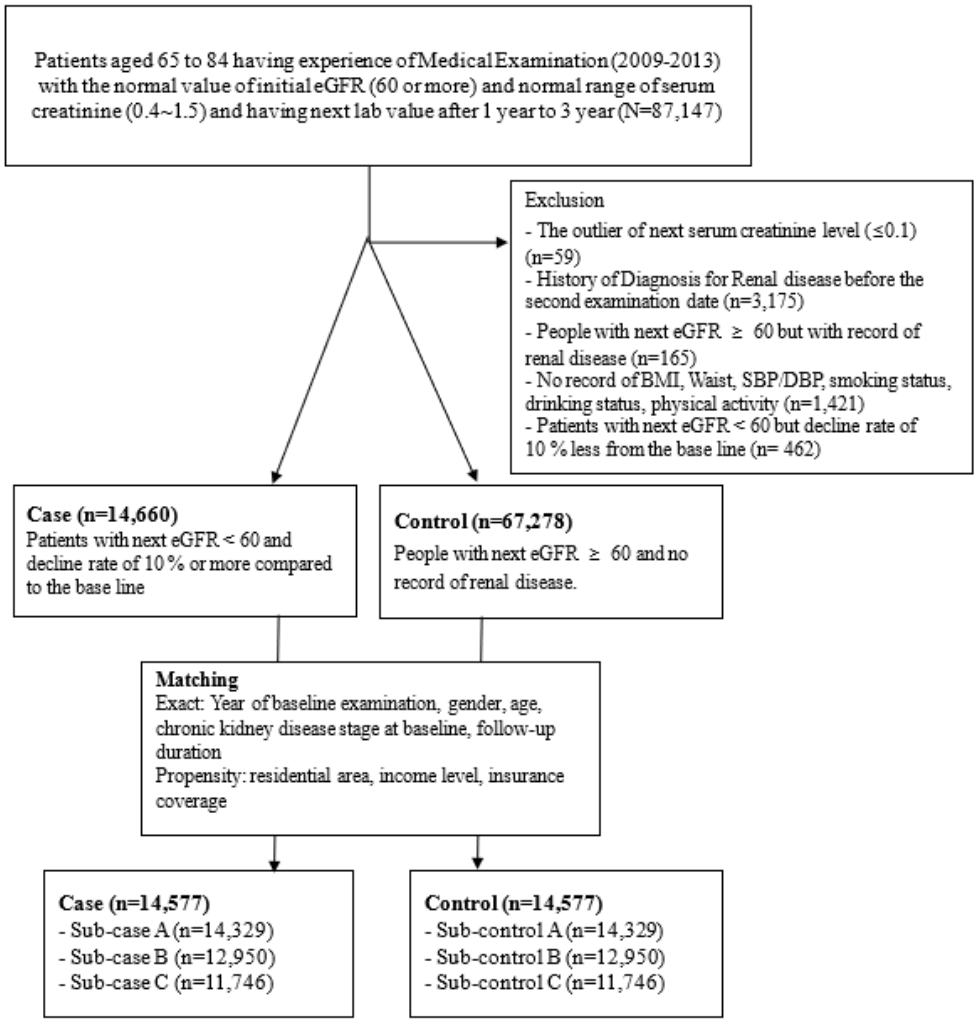

Figure 2. Flowcharts for Study Population (Study 1)

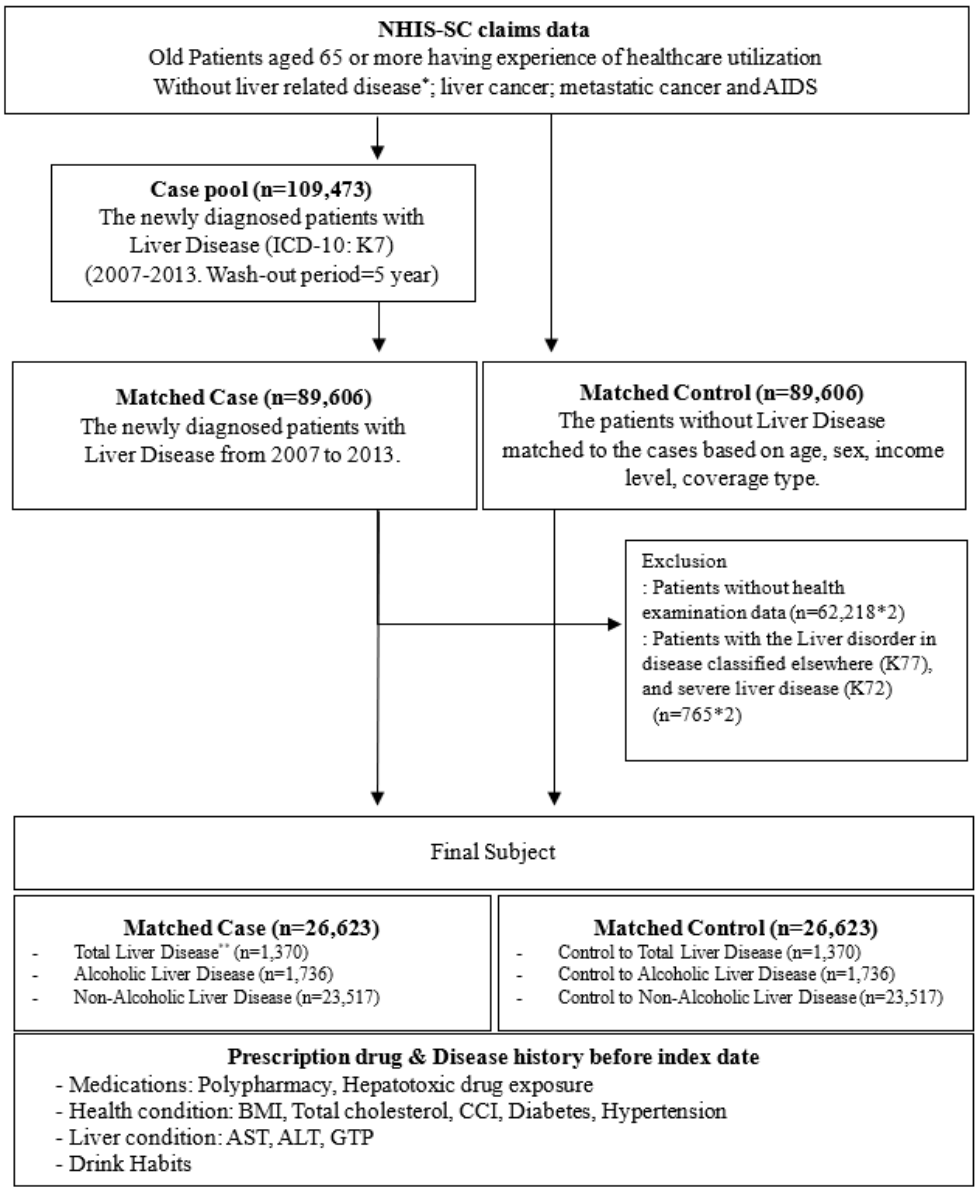

Figure 3. Flowcharts for Study Population (Study 2)

* viral hepatitis, hemochromatosis, jaundice NOS, Reye's syndrome, and Wilson's disease
** Total Liver disease except the infectious liver disease and severe status of failure

3. Study Model and Statistical Analysis

Baseline characteristics of the cases and controls were compared using a t-test for continuous variables and Chi-square test for categorical variables. Conditional logistic regression was used to calculate the odds ratio (OR) and its 95% confidence intervals (CIs) for matched pairs of cases and controls. All the risk factors were not matched between cases and controls but, instead, were included in adjusting models. After simple logistic analysis examining roughly the association between polypharmacy and clinical outcomes, multiple logistic analysis was performed by adjusting other risk factors such as disease-specific, medications, lifestyle-related. Specific covariates used in studies were different.

(1) The Effects of Polypharmacy on Kidney Dysfunction

Conditional logistic regression was used, and risk factors were adjusted step by step. First, the disease and lifestyle risk factors were included in the adjusted model. Second, only exposure to medication-related factors was considered. Third, as the final model in this study, all the risk factors were included. Subgroup analysis were conducted incorporating different definitions of kidney dysfunction into the final model.

(2) The Effects of Polypharmacy on Liver Disease

Conditional logistic regression was used, and causal mediation analysis was conducted step by step. First, not considering the exposure to hepatotoxic drugs as moderator and/or mediator, polypharmacy was mainly considered for the association with the liver disease using either simple and/or multiple analysis. Second, the moderation effect of exposure to hepatotoxic drugs was examined for the association between polypharmacy and liver diseases. Third, the mediation effect of the exposure to the hepatotoxic drugs was investigated and the direct and indirect effects of polypharmacy on the liver diseases were determined. (Refer to Figure 4)

Instead of using traditional mediation analysis, adjusted for the mediator in standard regression model with limitations caused by the interaction effect of exposure and mediator, causal mediation analysis was used to deal with causality and to estimate direct and indirect effects. Because it could be used even as there was an interaction between the exposure and mediator on the outcome and that could also be used in the non-linear models.

Under four assumptions**, the counterfactual definitions in direct and indirect effects can lead to causal inference. In this

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** (a) no unmeasured treatment-outcome confounding; (b) no unmeasured mediator-outcome confounding; (c) no unmeasured treatment-mediator confounding; and (d) no mediator-outcome confounder affected by treatment.

study with a binary outcome and binary mediator, the regression equations for the logistic model, the conditional direct effect (CDE), the natural direct effect (NDE), and the natural indirect effect (NIE) on the OR scale are then expressed as followings:

$$logit[P(Y=1 \mid Poly,TXE,c)] = \theta_0 + \theta_1 \cdot Poly + \theta_2 \cdot TXE + \theta_3 \cdot Poly \cdot TXE + \theta_4 \cdot c$$

$$logit[P(TXE=1 \mid Poly,c)] = \beta_0 + \beta_1 \cdot Poly + \beta_2 \cdot c$$

$$OR^{CDE} = (\theta_1 + \theta_3 \cdot TXE) \cdot (p - p')$$

$$OR^{NDE} \cong \frac{\exp(\theta_1 \cdot p)\{1 + \exp(\theta_2 + \theta_3 \cdot p + \beta_0 + \beta_1 \cdot p' + \beta_2 \cdot c)\}}{\exp(\theta_1 \cdot p')\{1 + \exp(\theta_2 + \theta_3 \cdot p' + \beta_0 + \beta_1 \cdot p' + \beta_2 \cdot c)\}}$$

$$OR^{NIE} \cong \frac{\{1 + \exp(\beta_0 + \beta_1 \cdot p' + \beta_2 \cdot c)\}\{1 + \exp(\theta_2 + \theta_3 \cdot p + \beta_0 + \beta_1 \cdot p + \beta_2 \cdot c)\}}{\{1 + \exp(\beta_0 + \beta_1 \cdot p + \beta_2 \cdot c)\}\{1 + \exp(\theta_2 + \theta_3 \cdot p + \beta_0 + \beta_1 \cdot p' + \beta_2 \cdot c)\}}$$

- The controlled direct effect (CDE) is the difference in effect comparing polypharmacy levels when exposure to the hepatotoxic drugs fixes at a level.
- The natural direct effect (NDE) is the difference between the counterfactual outcomes at different polypharmacy levels when the value of the exposure to hepatotoxic drugs is fixed at those without polypharmacy.
- The natural indirect effect (NIE) is the difference between the counterfactual outcomes at the two mediator levels, i.e. whether to exposure to hepatotoxic drugs or not, when exposure to polypharmacy.

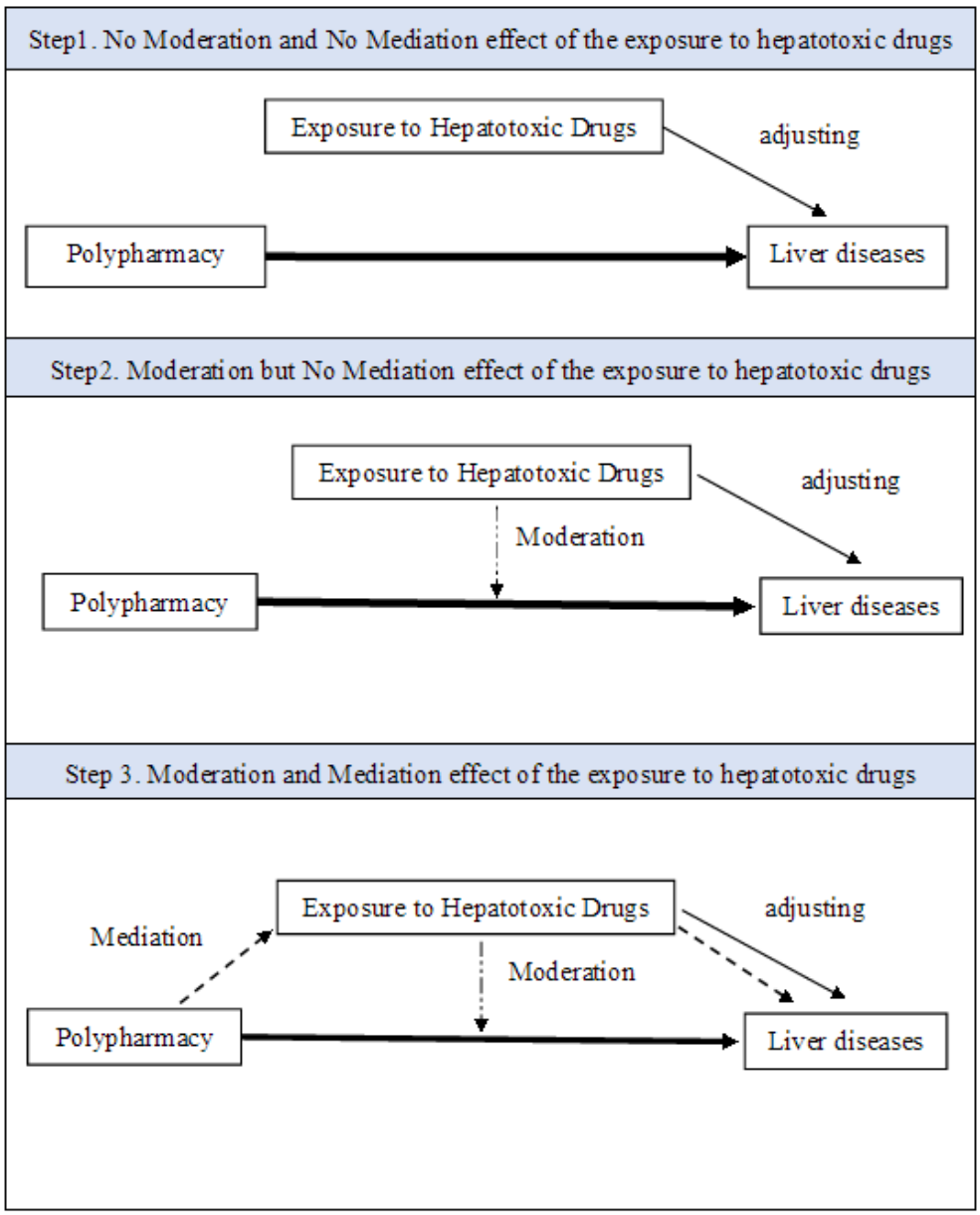

Figure 4. Steps for Mediation Analysis (Study 2)

4. Variables

Polypharmacy

Polypharmacy was computed based on the daily counts of pharmaceutical ingredients of all prescription drugs a year prior to the case's event date and subsequently classified into non-polypharmacy (N-PP, daily use of less than five), polypharmacy (PP, daily use of five to less than 10), and excessive polypharmacy (E-PP, daily use of 10 or more).

The prescription drugs included all the drugs covered by the NHIS from dental to medical care as well as inpatient and outpatient care. The NHIS formulary is comprehensive since it only excludes some of the new drugs that do not meet the cost-effectiveness criteria. However, OTC drugs, traditional medicines, and drugs absent in the NHIS formulary were not dealt with. Besides, parenteral medicines were not included in this study. When it comes to fixed-dose combination drugs, several pharmaceutical ingredients were counted except digestives and fillers.

Daily use counts of pharmaceutical ingredients per year, N

$$N = \frac{\sum(K_i * days\ of\ supply_i)}{1\ year}$$

- *Ki is the number of active pharmaceutical ingredients of a prescription drug i.*
- *N is five to less than ten for polypharmacy; and ten or more for excessive polypharmacy.*

An exposure period of a year is suitable for examining the associations of health outcomes in this study. Although, the excessive number of drugs in a short period would be critical for the kidneys and/or liver. Incident cases are discovered from regular check-up or healthcare visits rather than acute symptoms. Furthermore, defining polypharmacy for a year is more efficient when used to intervene in problems with a social perspective. To determine the appropriate duration for exposure to polypharmacy, sensitivity analyses were performed with different periods. (Refer to Supplementary Figure S1)

(1) The Effects of Polypharmacy on Kidney Dysfunction

Kidney Dysfunction

Glomerular filtration rate (GFR) is regarded as the best indicator for kidney function and is the reference criterion for classifying kidney disease established by the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative [52]. The cut-off point of 60 for GFR indicates chronic kidney disease [52]. Kidney dysfunction is operationally defined as the status of having GFR lower than 60ml/min/1.73m ^{2} while having a decline rate of 10% or more from baseline GFR. This decline rate excluded patients with little difference in the GFR between two health check-ups. Additionally, literature reports that annual decline rate can predict kidney disease progress [53]. Accordingly, annual eGFR decline rates of 3, 4, and 5 ml/min/1.73 m^2/year also used when defining kidney dysfunction in separate subgroup analysis.

It is common to use the eGFR from SCr concentration [54,55]. This study used the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation to estimate GFR. It is preferred for estimating GFR in adults because of its accuracy [56,57]. (Refer to Supplementary Table S2)

Other Risk Factors Adjusted in Study 1

A wide range of well-known kidney dysfunction risk factors were identified from literature and classified into disease-specific, medication-specific, and lifestyle-related risk factors. The disease-specific risk factors were hypertension (HTN) [58-69], diabetes mellitus (DM) [58-63,66,70], congestive heart failure (CHF) [62,71-73], ischemic heart disease (IHD) [62], arrhythmia [62], gout [74], hypercholesterolemia (Hyper-TC) [61,62,75], hypertriglyceridemia (Hyper-TG) [61-63,75,76], lower high density lipoprotein cholesterol (Lower-HDL-C) [61-63,75,77], higher low density lipoprotein cholesterol (Higher-LDL-C) [62,75,77], and obesity [58,60,70,78-82]. The medication-specific risk factors were angiotensin-converting-enzyme inhibitors (ACEIs) [83-86], angiotensin II receptor blockers (ARBs) [83-87], metformin [88], statins [89], non-steroidal anti-inflammatory drugs (NSAIDs) [70,83-86,90,91], proton pump inhibitors (PPIs) [84,85,92-94], and allopurinol [83,85,95]. The lifestyle-related risk factors were smoking [58,59,61-63,70,79,96-99], alcohol consumption [61,63,96,100,101], and physical activity [63,79,102-105].

Disease-specific risk factors were mainly determined based on the diagnosis code—based on the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10)—whether people had had the relevant disease code since the baseline to the case' s event date: HTN

(I10-I15); DM (E10-E14); CHF (I50); IHD (I20-I25); arrhythmia (I49); and gout (M10). Obesity was based on Body Mass Index (BMI) and classified into underweight (less than 18.5), normal weight (18.5-22.9), overweight (23.0-24.9), and obese (more than 25), according to the Asia Pacific regional guidelines of the World Health Organization and International Obesity Task Force. All the definitions related to lipid status were based on fasting lipid measure. Hyper-TC was defined as total cholesterol level more than 240 mg/dL; Lower HDL-C as HDL-C≤40mg/dL; Higher LDL-C as LDL-C≥140mg/dL; and Hyper-TG as triglycerides ≥150mg/dL.

Exposure to each medication risk factor was defined depending on types of medication. First, exposure to chronic medicines (ACEIs, ARBs, Metformin, Statins) was defined based on a PDC (Proportion of Days Covered) of 50% or higher for a year prior to the case' s event date. Second, exposure to NSAIDs and PPIs was defined as above, using 90 days instead of one year. Third, exposure to allopurinol was defined based on a record of prescription two weeks prior to the event date.

Subsequently, smoking status was classified as smoker or non-smoker based on consecutive non-smoker responses at baseline as well as follow-up health check-ups to a question about whether a patient had smoked more than 5 boxes or 100 cigarettes in their lifespan. On the other hand, alcohol

consumption status was defined based on the mean number of drinking days per week (non-drinker: 0-1 day per week) for the responses at base line and follow-up. The exercise status was also defined based on the mean number of exercise days per week for the responses at base line and follow-up, in which each patient performed moderate physical activity for at least 30 minutes (non-exerciser: 0-1 day per week).

Risk Factors for Kidney Dysfunction	
Disease specific	Hypertension (HTN); Diabetes Mellitus (DM); Congestive Heart Failure (CHF); Ischemic Heart Disease (IHD); Arrythmia; Gout
	Body mass index (BMI); Total Cholesterol (TC); Triglyceride (TG) ; High-Density Lipoprotein Cholesterol (HDL-C); Low-Density Lipoprotein Cholesterol (LDL-C)
Medication	Angiotensin-Converting-Enzyme Inhibitor (ACEI); Angiotensin II Receptor Blocker (ARB); Metformin; Statins; NSAIDs; Acetaminophen; Proton Pump Inhibitors (PPIs), Allopurinol; Antibiotics (vancomycin, penicillin, cephem, macrolide, amphenicol, fluoroquinolone, sulfonamides, fosfomycin etc.); Osmotic agents; Contrast; Methotrexate (MTX); Calcineurin inhibitors.
Life style	Smoking; Drinking status; Physical activity

Figure 5. Risk Factors for Kidney Dysfunction (Study 1)

See Supplementary Table S3 for Details.
*Antibiotics, Osmotic agents, Contrasts, MTX, and Calcineurin inhibitors were not included in main analysis because of non-practical differences

(2) The Effects of Polypharmacy on Liver Disease

Liver Disease

According to the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10), cases of liver disease were defined as the newly diagnosed patients with liver diseases (ICD 10: K70, K71, K73-K76) from 2007 to 2013. The new patients are regarded as the patients without a prior diagnosis of liver disease (ICD 10: K7-) for 5 years.

Liver disease in disease classified elsewhere (ICD 10: K77) and severe status of hepatic failure (ICD: K72) were not included. The reason for the latter also being excluded was that it may have more causes than polypharmacy for a year. As for the former, liver diseases of K77 were excluded because they had already been discovered as infectious and parasitic diseases and not caused by polypharmacy. However, toxic liver disease and alcoholic liver disease were included to examine whether they have a synergistic effect with polypharmacy apart from toxins and/or alcohol.

Therefore, the total cases for liver disease were included in the main analysis, followed by subgroup analysis of different types of liver disease including toxic liver disease, alcoholic liver disease and non-alcoholic liver disease.

Types of Liver Disease	Specific name of disease with ICD 10 code
Total Liver Disease*	Include all the liver disease as mentioned below.
- Toxic Liver Disease	K71. Toxic liver disease
- Alcoholic Liver Disease	K70. Alcoholic Liver disease
- Non-alcoholic Liver Disease	K73. Chronic hepatitis, not elsewhere classified K74. Fibrosis and cirrhosis of liver K75. Other inflammatory liver diseases K76. Other diseases of liver

Figure 6. Types of Liver Disease included (Study 2)

*Total Liver disease except the infectious liver disease and severe status of failure: Hepatic failure, not elsewhere classified(K72) and Liver disorders in disease classified elsewhere (K77) were not included.

Hepatotoxic Drugs

To confirm the relation between polypharmacy and liver diseases, it is important to understand the role of hepatotoxic drugs. The exposure to hepatotoxic drugs was determined by whether they were prescribed one week before the event because the average duration between the suspected drug exposure and the idiosyncratic reactions is about 1-2 weeks to at most 3 months[106,107] The hepatotoxic drug list was made by referring to the research conducted by Suzuki et al. [41], which developed a unified list based on the International Collaborative Work using three registries from Spain, Sweden, and U.S. (Supplementary Table S4)

Other Risk Factors Adjusted in Study 2

Other previously unused covariates have also been considered as matching variables in this study model using the disease code in the claims data and laboratory values. The answers for questionnaires in the health examination data under two years are: disease condition based on diagnosis (Charlson Comorbidity Index, CCI; Hypertension, and Diabetes mellitus) and health examination data (Obesity; Hyper Total Cholesterol, Hyper-TC), prior abnormal condition of liver enzyme (AST, ALT and gamma GTP) and habits of alcohol consumption.

Diseases based on diagnosis were mainly determined according ICD-10, whether people had had the relevant disease code or not during 2 years before the case's event date. Hypertension (I10-I15), Diabetes Mellitus (E10-E14), and Charlson Comorbidity Index (CCI) was calculated and classified into three categories—normal (CCI score of 0 and 1), mild disease (CCI score of 2, 3, 4), and severe disease (CCI score of 5 or more).

Obesity was based on Body Mass Index (BMI), and classified into underweight (less than 18.5), normal weight (18.5 -22.9), overweight (23.0-24.9), and obese (more than 25), according to the Asia Pacific regional guidelines of the World Health Organization and International Obesity Task Force. Hyper-TC was defined as the total cholesterol level more than

240 mg/dL. Abnormalities in liver enzyme were defined as: elevated AST was defined as AST more than 40, elevated ALT was defined as ALT more than 40 and elevated gamma GTP was defined as gamma GTP more than 63 for male, 35 for female.

Drinking habits were categorized into three levels based on the frequency of drinking per week: never (0 days); moderate (1~4 days); severe (5 days or more).

IV. Results

(1) The Effects of Polypharmacy on Kidney Dysfunction

Description of Study Sample

From the cases (n=14,657) and controls (n=67,278) that met the inclusion/exclusion criteria in the cohort, the matches resulted in 14,577 pairs of cases and controls. Before matching, cases and controls were different for every variable except insurance type. However, after matching, cases and controls were well-balanced with practically no differences. In fact, cases and controls were identical, except for income and residential areas (see Supplementary Table S5 for details).

As seen in the study sample description, exposures to polypharmacy (PP) and excessive polypharmacy (E-PP) were higher among cases than controls: 33.15% vs. 25.23% respectively for PP and 8.49% vs. 4.98% for E-PP. Exposure to the other risk factors were also significantly higher among cases than controls except for Hyper-TC, Higher-LDL-C, smoking, and physical activity. (Table 1)

Table 1. Description of Study Population (Study 1)

		Matched Case (n=14,577)		Matched Control (n=14,577)		p-value
		Freq.	(%)	Freq.	(%)	
Polypharmacy						
N-PP		8,507	58.36	10,173	69.79	<.0001
PP		4,832	33.15	3,678	25.23	
E-PP		1,238	8.49	726	4.98	
Disease-specific						
HTN		9,913	68.00	8,245	56.56	<.0001
DM		3,856	26.45	2,941	20.18	<.0001
CHF		623	4.27	364	2.50	<.0001
IHD		2,105	14.44	1,541	10.57	<.0001
Arrhythmia		271	1.86	192	1.32	0.0002
Gout		367	2.52	168	1.15	<.0001
Obesity level	Underweight	414	2.84	635	4.36	<.0001
	Normal weight	4,817	33.05	5,453	37.41	
	Overweight	3,840	26.34	3,773	25.88	
	Obese	5,506	37.77	4,716	32.35	
Hyper-TC		1,977	13.56	1,907	13.08	0.2280
Hyper-TG		5,303	36.38	4,488	30.79	<.0001
Lower-HDL-C		2,335	16.02	1,878	12.88	<.0001
Higher-LDL-C		3,566	24.46	3,577	24.54	0.8810
Medication-specific						
ACEIs		664	4.56	451	3.09	<.0001
ARBs		5,401	37.05	3,615	24.80	<.0001
Metformin		2,168	14.87	1,590	10.91	<.0001
Statins		3,301	22.65	2,619	17.97	<.0001
NSAIDs		2,641	18.12	2,294	15.74	<.0001
PPIs		885	6.07	699	4.80	<.0001
Allopurinol		62	0.43	25	0.17	<.0001
Lifestyle-related						
Smoking		4,705	32.28	4,599	31.55	0.1829
Drinking		4,075	27.95	4,220	28.95	0.0600
Physical activity		5,637	38.67	5,597	38.40	0.6300

Non-PP: Non-polypharmacy, use of less than five drugs; PP: Polypharmacy, use of five to 10 drugs; E-PP: Excessive polypharmacy, use of 10 or more drugs; HTN: hypertension; DM: diabetes mellitus; CHF: congestive heart failure; IHD: ischemic heart disease; Underweight: BMI < 18.5; Normal: BMI < 23; Overweight: BMI < 25; Obese: BMI ≥ 25; Hyper-TC: Hypercholesterolemia; Hyper-TG: hypertriglyceridemia; Lower-HDL-C: lower high density lipoprotein cholesterol; Higher-LDL-C: higher low density lipoprotein cholesterol; ACEIs: Angiotensin-Converting-Enzyme Inhibitors; ARBs: Angiotensin II Receptor Blockers; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs; PPIs: Proton Pump Inhibitors

Associative Risk of Kidney Dysfunction from Polypharmacy

Compared to controls without kidney dysfunction, cases with kidney dysfunction were significantly associated with higher odds of exposure to polypharmacy not only in the crude conditional logistic regression model (PP: OR=1.57, 95% CI= 1.49-1.66; E-PP: OR=2.07, 95% CI= 1.88-2.28) but also in each risk-adjusted model.

In Model 1, adjusting for the disease-specific and lifestyle-related risk factors, the adjusted OR was 1.29 (95% CI= 1.21-1.37) for polypharmacy and 1.60 (95% CI= 1.44-1.79) for excessive polypharmacy. In Model 2, adjusting for the medication risk factors, adjusted OR was 1.30 (95% CI=1.23-2.38) for polypharmacy and 1.59 (95% CI= 1.42 - 1.77) for excessive polypharmacy. Finally, in Model 3, the significant associations existed even after adjusting all the risk factors including disease-specific, life-style related risk, and medication risk factors (PP: aOR=1.21, 95% CI: 1.14 - 1.29; E-PP: aOR=1.46, 95% CI= 1.30 - 1.64).

Model 3, adjusted for all risk factors, showed significant positive associations between exposure to each risk factor and kidney dysfunction for all disease-related risk factors except IHD and arrhythmia. As for the medication-specific risk factors, only two medications were significantly associated with kidney dysfunction (ACEI: aOR =1.35, 95% CI = 1.18 - 1.54; ARB: aOR=1.45, 95%

CI = 1.36 - 1.54). Metformin and allopurinol were significantly associated in Model 2, but not when the other risk factors were adjusted. Finally, for the lifestyle-related risk factors, overweight people were more likely to have kidney dysfunction (normal weight: aOR=1.22, 95 % CI =1.06 - 1.40; overweight: aOR=1.28, 95% CI=1.11-1.48; obese: aOR =1.38, 95% CI: 1.20 - 1.58, ref=underweight). For lipid measures, Hyper-TG and Lower-HDL-C were significantly associated with kidney dysfunction (Hyper-TG: aOR = 1.17, 95% CI: 1.11 - 1.24; Lower-HDL-C: aOR = 1.17, 95% CI: 1.09 - 1.26; Higher-LDL-C: aOR = 1.00, 95% CI: 1.00 - 1.00). As for smoking, drinking, and physical activity, only smoking was significantly associated with kidney dysfunction (aOR: 1.08, 95% CI: 1.00 - 1.15) (Table 2).

Table 2. Associative Risk of Kidney Dysfunction from Polypharmacy

	Unadjusted			Adjusted								
				Model 1			Model 2			Model 3		
	OR	95 % CI		aOR	95 % CI		aOR	95 % CI		aOR	95 % CI	
Polypharmacy (ref=N-PP)												
PP	1.57	1.49	1.66	1.29	1.21	1.37	1.30	1.23	1.38	1.21	1.14	1.29
E-PP	2.07	1.88	2.28	1.60	1.44	1.79	1.59	1.42	1.77	1.46	1.30	1.64
Disease-specific												
HTN	-	-	-	1.34	1.27	1.41	-	-	-	1.14	1.07	1.21
DM	-	-	-	1.12	1.06	1.19	-	-	-	1.11	1.02	1.20
CHF	-	-	-	1.36	1.19	1.56	-	-	-	1.33	1.16	1.53
IHD	-	-	-	1.07	0.99	1.16	-	-	-	1.07	0.98	1.15
Arrhythmia	-	-	-	1.13	0.93	1.38	-	-	-	1.11	0.91	1.35
Gout	-	-	-	1.91	1.58	2.32	-	-	-	1.85	1.51	2.28
Normal-weight (ref=under-)	-	-	-	1.23	1.07	1.41	-	-	-	1.22	1.06	1.40
Over-weight (ref=under-)	-	-	-	1.30	1.13	1.50	-	-	-	1.28	1.11	1.48
Obese (ref=under)	-	-	-	1.41	1.23	1.62	-	-	-	1.38	1.20	1.58
Hyper-TG	-	-	-	1.17	1.11	1.24	-	-	-	1.17	1.11	1.24
Lower-HDL-C	-	-	-	1.17	1.09	1.25	-	-	-	1.17	1.09	1.26
Hyper-LDL-C	-	-	-	1.00	1.00	1.00	-	-	-	1.00	1.00	1.00
Medication-specific												
ACEI	-	-	-	-	-	-	1.44	1.27	1.64	1.35	1.18	1.54
ARB	-	-	-	-	-	-	1.59	1.51	1.69	1.45	1.36	1.54
Metformin	-	-	-	-	-	-	1.09	1.01	1.17	0.99	0.89	1.09
Statins	-	-	-	-	-	-	1.02	0.96	1.09	0.97	0.91	1.04
NSAIDs	-	-	-	-	-	-	1.05	0.99	1.12	1.04	0.97	1.11
PPI	-	-	-	-	-	-	1.08	0.97	1.21	1.09	0.98	1.22
Allopurinol	-	-	-	-	-	-	2.01	1.25	3.23	1.18	0.69	2.01
Lifestyle-related												
Smoking	-	-	-	1.07	1.00	1.15	-	-	-	1.08	1.00	1.15
Drinking	-	-	-	0.97	0.91	1.03	-	-	-	0.96	0.90	1.02
Physical activity	-	-	-	1.02	0.97	1.07	-	-	-	1.02	0.97	1.07

Non-PP: Non-polypharmacy for daily counts of less than 5 drugs per year; PP: Polypharmacy for daily counts of 5-10 drugs per year; E-PP: Excessive polypharmacy for daily counts of 10 or more drugs per year; HTN: hypertension; DM: diabetes mellitus; CHF: congestive heart failure; IHD: ischemic heart disease; Underweight: BMI < 18.5; Normal: BMI < 23; Overweight: BMI < 25; Obese: BMI ≥ 25; Hyper-TG: hypertriglyceridemia; Lower-HDL-C: lower high density lipoprotein cholesterol; Higher-LDL-C: higher low density lipoprotein cholesterol; ACEIs: Angiotensin-Converting-Enzyme Inhibitors; ARBs: Angiotensin II Receptor Blockers; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs; PPIs: Proton Pump Inhibitors

Subgroup Analysis for Different Definitions of Kidney Dysfunction

Several subgroups of cases and controls were generated using different definitions to deal with the uncertainty of defining kidney dysfunction. Contrary to the definition in the original model, subgroups using annual, rather than total decline rate, were constructed. Sub-case A consisted of patients whose next eGFR was less than 60, with an annual decline rate of 3 ml/min/1.73m^2 or more. The matched controls were sub-control A (each N=14,329). Sub-case/control B (each N=12,950) and sub-case/control C (each N=11,746) were defined using the annual decline rates of 4 ml/min/1.73m^2 or more and 5 ml/min/1.73m^2 or more respectively.

Across different definitions of kidney dysfunction, the significant associations between polypharmacy and kidney dysfunction were confirmed consistently from not only simple analysis but also multiple analysis.

All other risk factors had the same significant association with kidney dysfunction as the original analysis, except that the use of PPI was also significantly associated with kidney dysfunction, with aOR of 1.21 (95% CI: 1.00 - 1.25) for subgroup A, 1.14 (95% CI: 1.02 - 1.28) for subgroup B, and 1.16 (95% CI: 1.03 - 1.31) for subgroup C. (Table 3)

Table 3. Subgroup Analysis for Associative Risk of Kidney Dysfunction from Polypharmacy

	Subgroup A			Subgroup B			Subgroup C		
	OR	95 % CI		OR	95 % CI		OR	95 % CI	
Unadjusted Model									
PP (ref=N-PP)	1.57	1.49	1.66	1.57	1.49	1.67	1.62	1.53	1.72
E-PP (ref=N-PP)	2.07	1.88	2.28	2.10	1.91	2.30	2.22	1.98	2.47
Adjusted Model									
PP (ref=N-PP)	1.22	1.15	1.30	1.23	1.15	1.32	1.24	1.16	1.33
E-PP (ref=N-PP)	1.47	1.31	1.65	1.53	1.35	1.72	1.55	1.37	1.76
Disease-specific									
HTN	1.14	1.07	1.22	1.14	1.07	1.22	1.17	1.10	1.26
DM	1.11	1.02	1.20	1.12	1.03	1.23	1.12	1.02	1.22
CHF	1.33	1.16	1.53	1.34	1.15	1.55	1.30	1.12	1.52
IHD	1.06	0.98	1.15	1.04	0.95	1.13	1.04	0.95	1.14
Arrhythmia	1.11	0.91	1.36	1.18	0.95	1.46	1.20	0.96	1.49
Gout	1.81	1.47	2.23	1.65	1.32	2.06	1.69	1.34	2.12
Normal weight (Ref=Under-)	1.21	1.05	1.39	1.17	1.02	1.36	1.17	1.00	1.36
Over-weight (Ref=Under-)	1.27	1.10	1.46	1.24	1.07	1.44	1.23	1.06	1.44
Obese (Ref=Under-)	1.37	1.19	1.58	1.34	1.15	1.55	1.32	1.14	1.54
Hyper-TG	1.17	1.11	1.24	1.18	1.12	1.25	1.16	1.10	1.23
Lower-HDL-C	1.19	1.10	1.27	1.17	1.08	1.26	1.20	1.11	1.30
Hyper-LDL-C	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Medication-specific									
ACEI	1.37	1.20	1.56	1.34	1.17	1.55	1.29	1.12	1.49
ARB	1.43	1.35	1.53	1.45	1.35	1.55	1.43	1.33	1.53
Metformin	0.99	0.90	1.10	1.01	0.91	1.13	1.02	0.91	1.14
Statins	0.97	0.91	1.04	0.97	0.91	1.04	0.97	0.90	1.04
NSAIDS	1.05	0.98	1.12	1.05	0.98	1.13	1.06	0.99	1.14
PPI	1.12	1.00	1.25	1.14	1.02	1.28	1.16	1.03	1.31
Allopurinol	1.20	0.65	1.92	1.27	0.72	2.23	1.42	0.78	2.59
Lifestyle-related									
Smoking	1.08	1.00	1.16	1.12	1.03	1.20	1.12	1.04	1.22
Drinking	0.97	0.91	1.30	0.96	0.89	1.02	0.97	0.90	1.04
Physical activity	1.01	0.96	1.06	1.00	0.95	1.06	1.01	0.95	1.07

Non-PP: Non-polypharmacy for daily counts of less than 5 drugs per year; PP: Polypharmacy for daily counts of 5-10 drugs per year; E-PP: Excessive polypharmacy for daily counts of 10 or more drugs per year; HTN: hypertension; DM: diabetes mellitus; CHF: congestive heart failure; IHD: ischemic heart disease; Underweight: BMI < 18.5; Normal: BMI < 23; Overweight: BMI < 25; Obese: BMI ≥ 25; Hyper-TG: hypertriglyceridemia; Lower-HDL-C: lower high density lipoprotein cholesterol; Higher-LDL-C: higher low density lipoprotein cholesterol; ACEIs: Angiotensin-Converting-Enzyme Inhibitors; ARBs: Angiotensin II Receptor Blockers; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs; PPIs: Proton Pump Inhibitors

(2) The Effects of Polypharmacy on Liver Disease

Demographics

The case of final subject—the patients newly diagnosed with liver disease during 2007 to 2013—amounted to 26,623. Among the selected case groups, females constituted more than half (54.28%). As for the age groups, they mainly comprised of patients aged 65 to 74 (69.75%) and 75 to 84 (28.96%). Because the control groups were matched to cases based on income level, coverage type, residential area as well as gender and age group, those characteristics between case and control were well-balanced with no practical differences. (Refer to Supplementary Table S6)

As seen in the description of study population, the exposure to polypharmacy was higher in the case group (21.99% for PP; and 3.65% for E-PP) than in the control group (19.48% for PP; and 2.54% for E-PP). The exposure to hepatotoxic drugs was also higher in the case group (20.28%) than in the control group (12.52%). Other risk factors for liver disease were also significantly higher among the case groups and were adjusted in the risk adjustment models. (Table 4)

Table 4. Description of Study Population (Study 2)

		Matched Case (n=26,623)		Matched Control (n=26,623)		p-value
		Freq.	(%)	Freq.	(%)	
Polypharmacy						
N-PP		19,798	74.36	20,759	77.97	<.0001
PP		5,854	21.99	5,187	19.48	
E-PP		971	3.65	677	2.54	
Medication-specific						
Hepatotoxic drugs		5,400	20.28	3,333	12.52	<.0001
Disease-specific						
Health condition	Normal	17,611	66.15	19,061	71.60	<.0001
	Mild	8,168	30.68	6,733	25.29	
	Severe	844	3.17	829	3.11	
HTN		15,906	59.75	15,151	56.91	<.0001
DM		7,023	26.38	6,022	22.62	<.0001
Hyper-TC		3,866	14.52	3,570	13.41	0.00
Obesity level	Underweight	969	3.64	1,317	4.95	<.0001
	Normal	9,273	34.83	10,149	38.12	
	Overweight	6,940	26.07	6,610	24.83	
	Obese	9,441	35.46	8,547	32.10	
Abnormal Liver function	AST	2,860	10.74	1,330	5.00	<.0001
	ALT	2,842	10.67	1,239	4.65	<.0001
	Gamma GTP	4,769	17.91	2,688	10.10	<.0001
Lifestyle-related						
Drink Habit	Never	20,793	78.10	22,170	83.27	<.0001
	Moderate	2,701	10.15	2,128	7.99	
	Severe	3,129	11.75	2,325	8.73	

N-PP: Non-polypharmacy for daily counts of less than 5 drugs per year; PP: Polypharmacy for daily counts of 5-10 drugs per year; E-PP: Excessive polypharmacy for daily counts of 10 or more drugs per year; Health condition was based on Charlson Comorbidity Index (CCI) and classified into three categories: normal (CCI score of 0 and 1), mild disease (CCI score of 2, 3, 4), and severe disease (CCI score of 5 or more); HTN: hypertension; DM: diabetes mellitus; Hyper-TC: Hypercholesterolemia; Obesity level was based on Body Mass Index (BMI) and classified into four categories: Underweight: BMI < 18.5; Normal: BMI < 23; Overweight: BMI < 25; Obese: BMI ≥ 25; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GTP: glutamate pyruvate transaminase

Association between Polypharmacy and Liver Disease

Cases with liver disease were significantly associated with higher odds of exposure to polypharmacy (PP: OR= 1.19, 95% CI = 1.14-1.24; E-PP: OR= 1.51; 95% CI = 1.37 - 1.68) based on the results from a simple analysis. However, the association between polypharmacy and liver diseases was attenuated after adjusting other covariates (PP: aOR= 1.05, 95% CI = 1.00 - 1.10; E-PP: aOR= 1.25; 95% CI= 1.12 - 1.40).

Some covariates are significantly associated with the liver diseases: patients with moderate health condition (aOR=1.24, 95% CI=1.19-1.30, ref=normal health condition), patients with hyper total cholesterol (aOR=1.06, 95% CI=1.01-1.12). Increased obesity is also directly associated with higher likelihood of liver diseases (normal weight: aOR=1.23, 95% CI=1.12-1.34; overweight: aOR=1.38, 95% CI=1.26 - 1.52; obese: aOR=1.37, 95% CI=1.25-1.50, ref=underweight). People with an abnormal liver function before index dates are more likely to have liver diseases (AST: aOR=1.44, 95% CI=1.32-1.57; ALT: aOR=1.64, 95% CI=1.50-1.79; gamma GTP: aOR=1.49, 95% CI=1.41-1.58). Finally, people who frequently drink alcohol risk liver disease (Moderate: aOR=1.39, 95% CI=1.30 - 1.48; Severe: aOR=1.42, 95% CI=1.33 - 1.51). (Table 5)

Moderation Effect of Exposure to Hepatotoxic Drugs on the Association

There was significant interaction between polypharmacy and hepatotoxic drug exposure (PP*TXE: beta=−0.28, SE=0.05, p<0.001; E−PP*TXE: beta=−0.21, SE=0.12, p=0.066). Interpreting it in the context of the conditional effect of polypharmacy on liver diseases, there were more significant associations between polypharmacy and liver disease among patients without exposure to hepatotoxic drug (PP: aOR=1.11, 95% CI=1.06−1.17; E−PP: aOR=1.32, 95% CI=1.16−1.50, ref=N−PP) than those with (PP: aOR=0.84, 95% CI=0.76−0.93; E−PP: aOR=1.07, 95% CI=0.88−1.29, ref=N−PP).

The odds of exposure to hepatotoxic drugs was higher than the multiple analysis in the previous step which not considered moderation effect (aOR=1.88, 95% CI = 1.77 - 2.00). However, the odds and significance of other covariates were the are the same as those from the multiple analysis of Step 1. (Table 5)

Table 5. Association between Polypharmacy and Liver Disease (Step 1), and Considering Moderation Effect of Hepatotoxic Drugs (Step 2)

Variables		Step 1			Step 2		
		OR	95% CI		OR	95% CI	
Conditional effect of Polypharmacy		**Simple analysis**			**Exposure to hepatotoxic drugs**		
Polypharmacy (ref=N-PP)	PP	1.19	1.14	1.24	0.84	0.76	0.93
	E-PP	1.51	1.37	1.68	1.07	0.88	1.29
Conditional effect of Polypharmacy		**Multiple analysis**			**Non-exposure to hepatotoxic drugs**		
Polypharmacy (ref=N-PP)	PP	1.05	1.00	1.10	1.11	1.06	1.17
	E-PP	1.25	1.12	1.40	1.32	1.16	1.50
Hepatotoxic drugs		1.71	1.63	1.80	1.88	1.77	2.00
Covariates							
Health condition (ref=normal)	Moderate	1.24	1.19	1.30	1.24	1.19	1.30
	Severe	1.02	0.92	1.14	1.02	0.92	1.14
HTN		0.98	0.95	1.02	0.98	0.94	1.02
DM		1.03	0.98	1.08	1.03	0.98	1.08
Hyper TC		1.06	1.01	1.12	1.06	1.01	1.12
Obesity (ref=under-weight)	Normal-	1.23	1.12	1.34	1.23	1.12	1.35
	Over-	1.38	1.26	1.52	1.38	1.26	1.52
	Obese	1.37	1.25	1.50	1.37	1.25	1.50
Abnormal Liver Function	AST	1.44	1.32	1.57	1.44	1.32	1.57
	ALT	1.64	1.50	1.79	1.64	1.50	1.79
	Gamma GTP	1.49	1.41	1.58	1.49	1.41	1.58
Frequently Drinking (ref=none)	Moderate	1.39	1.30	1.48	1.39	1.30	1.48
	Severe	1.42	1.33	1.51	1.42	1.33	1.52

N-PP: Non-polypharmacy for daily counts of less than 5 drugs per year; PP: Polypharmacy for daily counts of 5-10 drugs per year; E-PP: Excessive polypharmacy for daily counts of 10 or more drugs per year; Health condition was based on Charlson Comorbidity Index (CCI) and classified into three categories: normal (CCI score of 0 and 1), mild disease (CCI score of 2, 3, 4), and severe disease (CCI score of 5 or more); HTN: hypertension; DM: diabetes mellitus; Hyper-TC: Hypercholesterolemia; Obesity level was based on Body Mass Index (BMI) and classified into four categories: Underweight: BMI < 18.5; Normal: BMI < 23; Overweight: BMI < 25; Obese: BMI ≥ 25; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GTP: glutamate pyruvate transaminase

Mediation Effect of Exposure to Hepatotoxic Drugs on the Association

In mediation analysis, the interaction effect of hepatotoxic drugs and polypharmacy was included because it was identified in the analysis from Step 2. The results of the mediator model showed that increased exposure to polypharmacy lead to more expose to hepatotoxic drugs (aOR=3.81, 95% CI=3.60−4.03). In the outcome model, the total effect of polypharmacy on liver diseases was significant (aOR=1.06, 95% CI=1.03−1.08) even considering the exposure to hepatotoxic drugs as a mediator and/or moderator and adjusting other covariates. (Table 6)

After the decomposition of the total effect of polypharmacy on liver disease, however, the direct effect of polypharmacy was not significant anymore (aOR=1.00, 95% CI = 0.95 - 1.06). The effect of polypharmacy on liver disease mainly contributed to an indirect path through exposure to hepatotoxic drugs.

Table 6. Association between Polypharmacy and Liver Disease after Considering Mediation and Moderation Effect of Hepatotoxic Drugs (Step 3)

Variables		Mediator Model			Outcome Model		
		OR	95% CI		OR	95% CI	
Polypharmacy		3.81	3.60	4.03	1.06	1.03	1.08
− Natural Direct Effect		-	-	-	1.00	0.95	1.06
− Natural Indirect Effect		-	-	-	1.05	1.02	1.07
Interaction		-	-	-	0.94	0.92	0.96
Hepatotoxic Drugs		-	-	-	1.18	1.17	1.19
Covariates							
Health condition (ref=normal)	Moderate	0.81	0.72	0.92	1.01	0.98	1.03
	Severe	1.30	1.23	1.36	1.05	1.04	1.06
HTN		1.91	1.84	1.99	0.98	0.97	0.99
DM		1.08	1.02	1.14	1.00	0.99	1.02
Hyper-TC		1.23	1.17	1.30	1.01	1.00	1.03
Obesity (ref=under-weight)	Normal weight	1.68	1.53	1.84	1.06	1.04	1.08
	Overweight	1.53	1.39	1.68	1.06	1.04	1.08
	Obese	1.34	1.22	1.46	1.04	1.02	1.06
Abnormal Liver Function	AST	0.89	0.82	0.98	1.09	1.07	1.11
	ALT	1.10	1.01	1.21	1.11	1.09	1.13
	Gamma GTP	1.02	0.96	1.09	1.10	1.08	1.11
Frequently Drinking habit (ref=none)	Moderate	0.87	0.82	0.93	1.07	1.06	1.09
	Severe	0.98	0.92	1.05	1.07	1.06	1.09

Polypharmacy is regarded as the continuous variable from 0-2, 0 indicating N-PP, Non-polypharmacy for daily counts of less than 5 drugs per year; 1 indicating PP, Polypharmacy for daily counts of 5-10 drugs per year; 2 indicating E-PP: Excessive polypharmacy for daily counts of 10 or more drugs per year; Health condition was based on Charlson Comorbidity Index (CCI) and classified into three categories: normal (CCI score of 0 and 1), mild disease (CCI score of 2, 3, 4), and severe disease (CCI score of 5 or more); HTN: hypertension; DM: diabetes mellitus; Hyper-TC: Hypercholesterolemia; Obesity level was based on Body Mass Index (BMI) and classified into four categories: Underweight: BMI < 18.5; Normal: BMI < 23; Overweight: BMI < 25; Obese: BMI ≥ 25; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GTP: glutamate pyruvate transaminase

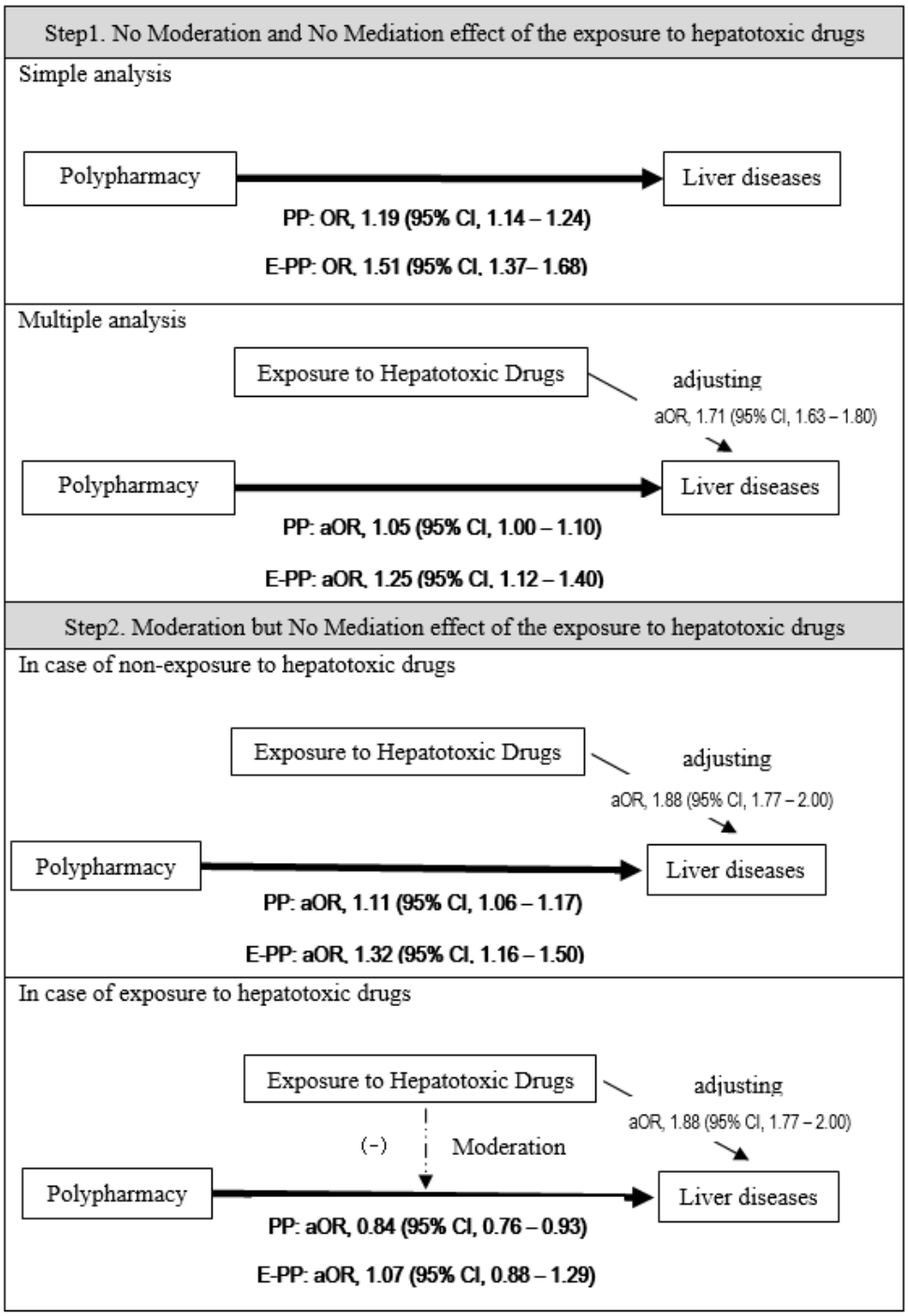

Figure 7. Association between Polypharmacy and Liver disease

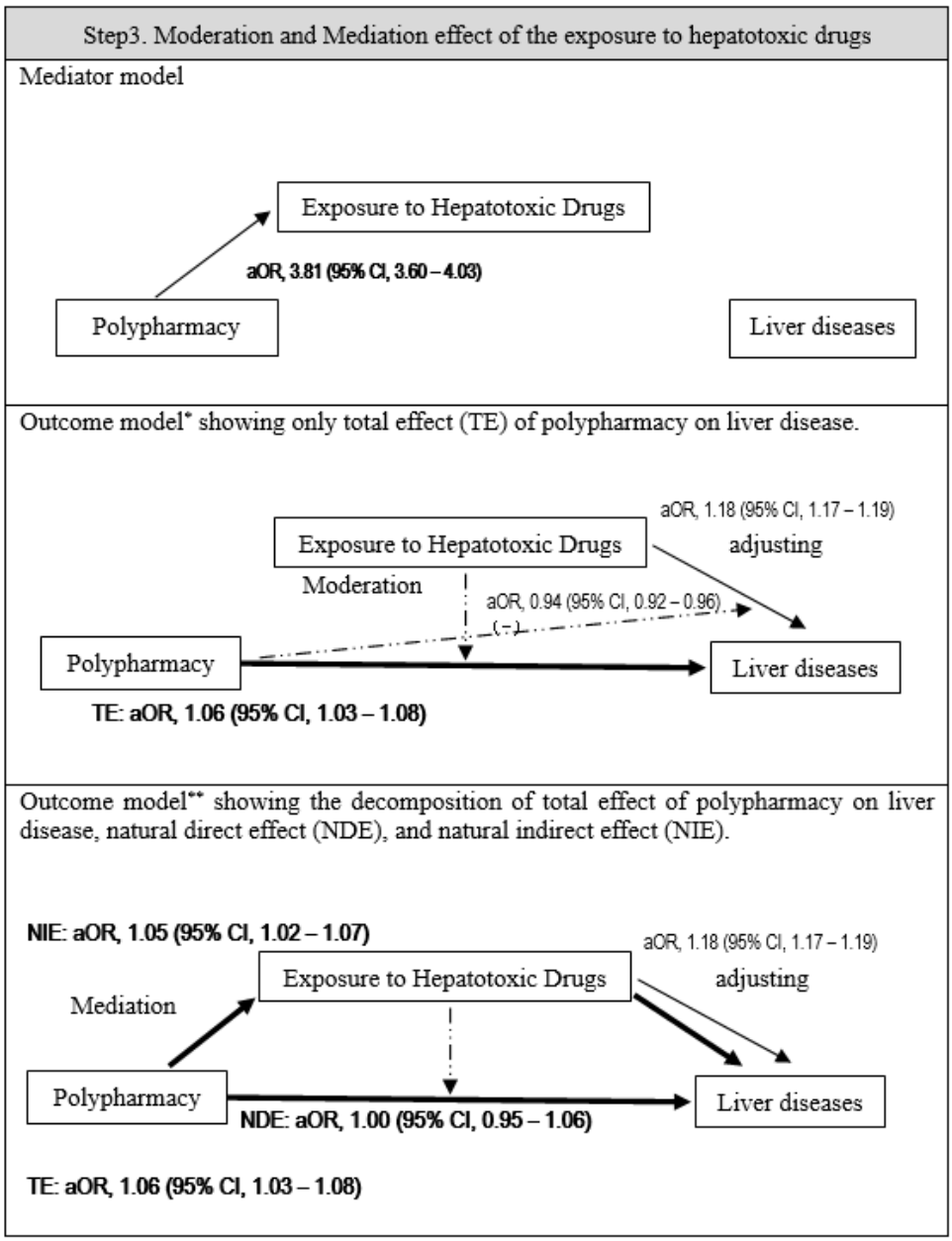

Figure 7. Association between Polypharmacy and Liver disease (continued)

*The Total effect (TE) of polypharmacy on liver disease was significant even adjusting the exposure to hepatotoxic drugs and its moderation effect and/or mediation effect on the association between polypharmacy and liver disease.
**After the decomposition of the total effect (TE) of polypharmacy on liver disease, direct effect (NDE) of polypharmacy was not significant. The indirect effect (NIE) of the exposure to hepatotoxic drugs was mainly accounted for the total effect.

Association between Polypharmacy and Other Liver Disease

The liver diseases analyzed in this study included toxic liver disease, alcoholic liver disease, and non-alcoholic liver disease which are not induced by toxin and alcohols. Sub-group analysis was performed assuming that the association with polypharmacy might differ according to specific types of liver diseases. However, toxic liver disease and alcoholic liver disease were excluded because they had not been significantly associated with polypharmacy, even in the simple analysis aside from any adjusting. (Supplementary Figure S1)

As for the non-alcoholic liver disease, the cases had higher odds of polypharmacy and excessive polypharmacy from simple analysis (PP: OR=1.19, 95% CI=1.14 - 1.25; E-PP: OR=1.61, 95% CI=1.44 - 1.79). After adjusting other covariates, the polypharmacy was not significant, but the excessive polypharmacy was still significantly associated with the disease (PP: aOR=1.04, 95% CI=0.99 - 1.09; E-PP: aOR=1.30, 95% CI=1.16 - 1.46). After considering the interaction between polypharmacy and the exposure to hepatotoxic drugs, the effect of polypharmacy on liver disease was only significant during non-exposure to hepatotoxic drugs (PP: aOR=1.10, 95% CI=1.04 - 1.17; E-PP: aOR=1.33, 95% CI=1.16 - 1.52).

In addition to the moderation effect, the role of the exposure to hepatotoxic drugs as a mediator was determined

while the direct effect of polypharmacy remained. (TE: aOR=1.06, 95% CI=1.03 - 1.09; NDE: aOR=1.02, 95% CI=1.01 - 1.04).

Table 7. Association between Polypharmacy and Non-Alcoholic Liver Disease

Variables \ Steps		Step 1			Step 2			Step 3		
		OR	95% CI		aOR	95% CI		aOR	95% CI	
Conditional effect of polypharmacy		**Simple analysis**			**Exposure to hepatotoxic drugs**			**Polypharmacy* (TE)**		
Polypharmacy (ref=N-PP)	PP	1.19	1.14	1.25	0.82	0.74	0.91	1.06	1.03	1.09
	E-PP	1.61	1.44	1.79	1.17	0.96	1.44	**Decomposition**		
Conditional effect of polypharmacy		**Multiple analysis**			**Non-exposure to hepatotoxic drugs**			**NDE (42.01%)**		
								1.02	1.01	1.04
Polypharmacy (ref=N-PP)	PP	1.04	0.99	1.09	1.10	1.04	1.17	**NIE (57.99%)**		
	E-PP	1.30	1.16	1.46	1.33	1.16	1.52	1.03	1.03	1.04
Hepatotoxic drugs		1.73	1.64	1.82	1.91	1.79	2.03	1.19	1.17	1.20
Covariates										
Health condition (ref=normal)	Moderate	1.23	1.18	1.29	1.23	1.18	1.29	1.00	0.98	1.03
	Severe	0.99	0.88	1.10	0.99	0.88	1.10	1.05	1.04	1.06
HTN		0.99	0.95	1.03	0.99	0.95	1.03	0.98	0.97	0.99
DM		1.06	1.01	1.12	1.06	1.01	1.12	1.01	1.00	1.02
Hyper-TC		1.07	1.02	1.13	1.08	1.02	1.14	1.01	1.00	1.03
Obesity (ref=under-)	Normal weight	1.26	1.14	1.39	1.26	1.14	1.39	1.07	1.05	1.09
	Overweight	1.42	1.28	1.57	1.42	1.29	1.57	1.07	1.04	1.09
	Obese	1.42	1.29	1.57	1.42	1.29	1.57	1.04	1.02	1.07
Abnormal Liver Function	AST	1.36	1.24	1.49	1.36	1.24	1.49	1.08	1.05	1.10
	ALT	1.72	1.56	1.89	1.72	1.56	1.89	1.12	1.10	1.15
	Gamma GTP	1.37	1.29	1.46	1.37	1.29	1.46	1.08	1.06	1.09
Frequently Drinking (ref=none)	Moderate	1.33	1.24	1.43	1.34	1.25	1.43	1.05	1.04	1.07
	Severe	1.27	1.18	1.36	1.27	1.18	1.37	1.07	1.05	1.09

*Polypharmacy is regarded as the continuous variable from 0-2, 0 indicating N-PP, Non-polypharmacy for daily counts of less than 5 drugs per year; 1 indicating PP, Polypharmacy for daily counts of 5-10 drugs per year; 2 indicating E-PP: Excessive polypharmacy for daily counts of 10 or more drugs per year.
Health condition was based on Charlson Comorbidity Index (CCI) and classified into three categories: normal (CCI score of 0 and 1), mild disease (CCI score of 2, 3, 4), and severe disease (CCI score of 5 or more); HTN: hypertension; DM: diabetes mellitus; Hyper-TC: Hypercholesterolemia; Obesity level was based on Body Mass Index (BMI) and classified into four categories: Underweight: BMI < 18.5; Normal: BMI < 23; Overweight: BMI < 25; Obese: BMI ≥ 25; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GTP: glutamate pyruvate transaminase; NDE, Natural Direct Effect; NIE, Natural Indirect Effect

V. Discussion

Polypharmacy is an important issue in Korea, especially with its fast-aging population. Previous studies have also determined the prevalence of polypharmacy in Korea. Kim et al. (2014)[11] reported that the prevalence of polypharmacy among geriatric patients was 86.4 %. However, these results are inconsistent with this study. In this study, the proportion of patients with polypharmacy (including excessive polypharmacy) among the case group was 41.64% and 25.97% while that of the control group was 30.21% and 22.13%, respectively for cases with kidney dysfunction and liver disease. This difference is caused by the different concepts and exposure durations, i.e., whether the case is being exposed to multiple drugs at least one day.

In terms of calculating polypharmacy, this dissertation's strength was its accuracy in drug utilization data and avoidance of the recall bias from a questionnaire-based study. However, it also had limitations—only the prescribed medicines from the NHIS formulary were included, and the information from prescription data was reflected rather than real taking while accounting for polypharmacy and medication related factors. Consequently, not considering the use of non-formulary drugs, drug samples, over-the-counter (OTC) drugs, supplements, and vitamins leads to underestimation of polypharmacy and a

restricted interpretation of its clinical consequences. It is crucial to consider the use of Korean herbal medicines while determining the potential risk of polypharmacy [108-112], especially among older patients, because such medication are preferred by geriatric patients in Korea [113,114]. However, the trend of using herbal medicine has declined since herbal medicine was not as affordable due to the non-coverage policy [115], and majority of drugs used by geriatric patients in Korea are prescribed medicines.

In observational studies that use health care utilization data, there might be protopathic bias [116]. It generally occurs when exposure is initiated in response to the outcome but it appears to cause the outcome, which is also called reversal causality [116]. Of course, in this study, patients with kidney dysfunction and/or liver disease are more likely to take more pharmaceuticals but they are also more cautious than the others while using multiple medicines. In addition, this dissertation had collected information from different time frame which exposes a precedent which was followed by the incident outcome. Therefore, the lag-time was not used. Not only the presence of exposure but also the precedence near the outcome is important to study the association between polypharmacy and kidney and/or liver.

This dissertation's key strengths are that it is one of the

first to investigate the organs where drugs are metabolized and excreted while considering clinical consequences from polypharmacy. According to review research [21,117], previous studies that identified outcomes related to polypharmacy—including increase in healthcare costs, hospitalization, non-adherence, adverse drug events, and pathological outcomes. Among the pathological outcomes, most of the studies focused on falls, fractures, functional status, and cognitive impairment including the disease of dementia [10,29-33,118-120], while the burden on the organs that metabolize and excrete the drugs have largely been overlooked. Additionally, the use of linked data from the health check-up information with prescription claims, which was constructed as cohort data under the universal health coverage system in Korea. Covariates were considered more than before due to the mandatory health examination by NHIS, which is the single payer and data provider in this study. Otherwise they would be confounders associated with health outcomes.

(1) The Effects of Polypharmacy on Kidney Dysfunction

Compared to the controls, whose normal kidney function was maintained since the baseline examination, the matched cases with kidney dysfunction had a higher exposure to polypharmacy as well as excessive polypharmacy (PP: 33.15 % vs. 25.23: E-PP: 8.49 % vs. 4.98%). The exposure to polypharmacy is higher among cases of kidney dysfunction than among controls with normal kidney function was also observed in the crude conditional logistic regression (PP: OR=1.57, 95% CI=1.49-1.66; E-PP: OR=2.07, 95% CI= 1.88-2.28) as well as the risk adjusted model (PP: aOR= 1.21, 95% CI= 1.14-1.29; E-PP: aOR=1.46, 95% CI= 1.30-1.64).

These results are consistent with the findings of three previous studies [36-38]. Konig et al. [38] reported a crude OR of 2.07 (95% CI: 1.54 - 2.74) and an adjusted OR of 1.54 (95% CI: 1.14 - 2.08) based on the Berlin Aging Study II (BASE -II) cohort. The other two studies also reported a significant association between polypharmacy and kidney dysfunction using different concepts of polypharmacy (duration of polypharmacy, polypharmacy of cardiovascular medicines) and focusing on kidney dysfunction of acute renal failure and injury. However, the results from this study were not consistent with Sutaria et al.' s study [39]. Their study found that polypharmacy negatively affects CKD, based on an unadjusted model. However, a

protective, though not statistically significant, effect of polypharmacy on CKD while adjusting for age, cardiovascular disease, and diabetes mellitus. There are some differences between the studies. First, their studies are cross-sectional while ours is a nested case control. Their studies did not control for the other important risk factors such as lifestyle-related and medication-specific. Furthermore, the effect of polypharmacy might be masked by the large variations in age, which was matched between cases and controls in our study. In other words, this study focused on risk factors for kidney dysfunction after exactly matching other covariates between cases and controls. Although various studies with slightly different operational definitions have examined the association between polypharmacy and kidney disease, they were all limited because they did not consider obesity and smoking, which are important risk factors for kidney function [36,37,39], or were biased due to using a self-reported questionnaire [38]. Consequently, considering the information available from our data, the risk factors for kidney disease considered and reflected in the study model are more varied than in other studies.

Moreover, the associated risks of polypharmacy, apart from exposure to polypharmacy for kidney dysfunction were identified: hypertension, diabetes, congestive heart failure, gout, obesity, hyper-TG, lower-HDL-C, smoking, and use of ACEIs/ARBs (as well as PPIs in a more rigorous sub-group).

Other nephrotoxic drugs including osmotic agents, contrast, methotrexate, calcineurin inhibitors, and certain antibiotics were not considered in the statistical model due to the limited number of takers and little difference between case and control groups resulting from basic statistical analysis. (Refer to Supplementary Table S5)

Interestingly, ACEIs/ARBs [70,83-87,90] were found to be significantly associated with kidney dysfunction despite the them being recommended as the first line of treatment hypertension for patients with a compelling condition of CKD [121-124] due to their reno-protective effect. Although it is initially tempting to claim that the adverse associations just reflect that patients who take ACEI/ARB are likely to have had kidney dysfunction, the associations from our case-control study provide a temporal sequence where exposure to ACEI/ARB precedes the outcome occurrence of kidney dysfunction. On the other hand, it is plausible that patients who take ACEI/ARB are likely to have had conditions of HTN/DM and, consequently, are more likely to develop kidney dysfunction, not from the medications but from the diseases. This study had a control for the presence of diseases in the risk adjustment model to separate the disease and medication specific effects, recognizing the potential confounding effects of HTN/DM. Consequently, our study found that the risk of kidney dysfunction was associated not only with the presence of HTN/DM but also with exposure to ACEI/ARB.

Our study is not the first to report that the use of ACEI/ARB may not always be reno-protective, especially in real world settings.[125-127]

The other risk factors known to damage kidneys but not found significant in this study are LDL, drinking, Proton Pump Inhibitors (PPIs), Metformin, Statin, and NSAIDs. However, plenty of evidence supports our study. Moreover, LDL is the least likely risk factor for kidney dysfunction among cholesterol types [70,77]. Additionally, drinking, especially moderate alcohol consumption, has no adverse effect on kidney function [128]. Accordingly, PPIs have the weakest level of evidence for being risk factors for kidney dysfunction [94]. PPIs were not significantly associated with kidney dysfunction in the main analysis of this study but were significantly associated in the subgroup analysis. Furthermore, literature suggests that Metformin [129,130] and Statin [131] are not associated with kidney function. Despite the widely-known adverse association of NSAIDs with kidney dysfunction [70,83-86,90], our study reports no such association. Thus, the contradictory findings may have resulted from two different study populations. While our study findings come from patients with normal kidney functioning, the findings in the literature are based on patients with kidney dysfunction. Alternatively, it is likely that the duration of NSAID exposure could affect the occurrence of reno-toxicity. Our study did not stratify NSAID exposure into long-term vs. short-term. Instead,

we divided NSAID exposure based on the proportion of days covered (PDC)—50% or higher for 90 days prior to the kidney dysfunction. While our study is not the first to report the contradictory finding,[132] [133] future studies need to examine whether the risk of reno-toxicity depends on long-term vs. short-term exposure to NSAID. Additionally, allopurinol is known to be reno-protective for hyperuricemia [95] but can also be reno-toxic for interstitial nephritis [70,83,85,86,90]. Allopurinol adversely affected the kidneys when not adjusted for gout in this study but it did not have an adverse effect when adjusted for gout. Consequently, future studies are required to understand this phenomenon as reflected by the comments of Stamp et al. [134]

(2) The Effects of Polypharmacy on Liver Disease

Compared to controls who had not developed liver disease, the matched cases with liver diseases had a higher exposure to polypharmacy as well as excessive polypharmacy (PP: 21.99 % vs. 19.48%; E-PP: 3.65 % vs. 2.54%). The significant association between polypharmacy and liver diseases were observed from a simple analysis (PP: OR= 1.19, 95% CI = 1.14-1.24; E-PP: OR= 1.51; 95% CI = 1.37 - 1.68). After adjusting other risk factors in multiple analysis, the association was attenuated (PP: aOR= 1.05, 95% CI = 1.00 - 1.10; E-PP: aOR= 1.25; 95% CI= 1.12 - 1.40).

Further, this study proved the role of exposure to hepatotoxic drugs in the association between polypharmacy and liver diseases as a moderator and/or mediator. First, there was significant interactive effect of hepatotoxic drug exposure on PP not E-PP (PP*TXE: beta=-0.28, SE=0.05, p<0.001; E-PP*TXE: beta=-0.21, SE=0.12, p=0.066). Interpreting it into the conditional effect of polypharmacy, it could increase the associated risk of liver disease due to non-exposure to hepatotoxic drugs (PP: aOR=1.11, 95% CI=1.06-1.17; E-PP: aOR=1.32, 95% CI=1.16-1.50) than when exposed to hepatotoxic drugs (PP: aOR=0.84, 95% CI=0.76-0.93; E-PP: aOR=1.07, 95% CI=0.88-1.29). There is a possibility of misinterpretation that there would be protective effect of exposure to hepatotoxic drugs on the association between polypharmacy and liver disease. However, it could be caused by the strong correlation between polypharmacy and hepatotoxic drugs. The potential association of polypharmacy was absorbed by the portion explained by exposure to hepatotoxic drugs. There would be no synergistic effect of polypharmacy and hepatotoxic drugs, but the effect of polypharmacy could increase the risk of liver disease despite non-exposure to hepatotoxic drugs.

The results of mediation analysis showed that the total effect of polypharmacy on liver diseases was significant (aOR=1.06, 95% CI=1.03-1.08), even considering the exposure

to hepatotoxic drugs as a mediator and/or moderator and adjusting other covariates. After the decomposition of total effect of polypharmacy on liver disease, however, the direct effect of polypharmacy was not significant anymore (aOR=1.00, 95% CI = 0.95 - 1.06). Besides, the effect of polypharmacy on liver disease mainly contributed to an indirect path through the exposure to hepatotoxic drugs. Polypharmacy was actually strongly associated with the exposure to hepatotoxic drugs (aOR=3.81, 95% CI=3.60-4.03 from mediator model).

Mediation analysis needs caution while interpreting results which is different from the other analysis that each effect of PP and E-PP compared to N-PP. While analyzing, the treatment variable of polypharmacy was regarded as the continuous variable with a range of 0 to 2 because treatment variables are restricted to over two categories in causal mediation analysis. Other variables were dealt with the same way as the other analyses. Because the polypharmacy was a continuous variable, information could be acquired about the average effect of a polypharmacy unit level: N-PP to PP, PP to E-PP.

The associations with polypharmacy differed depending on the types of liver disease. First, toxic liver disease and alcoholic liver disease were not significantly associated with polypharmacy, even in a simple analysis apart from any adjusting, which does not imply that there is no need to continue

to conduct analysis. They already had known causes for disease and there was no room for the additional effect of polypharmacy. In case of non-alcoholic liver disease, the results were almost like that of total liver disease, analyzed in main analysis, except that the direct effect of polypharmacy on non-alcoholic liver disease was greater total liver disease. This disease also had a negative direction in the interaction effect, which showed that the effect of polypharmacy on liver disease was only significant during non-exposure to hepatotoxic drugs. Finally, the role of the exposure to hepatotoxic drugs as mediator was also determined while the direct effect of polypharmacy still remained (TE: aOR=1.06, 95% CI=1.03 - 1.09; NDE: aOR=1.02, 95% CI=1.01 - 1.04).

There is a strong belief that certain drugs, known as hepatotoxic drugs, cause liver diseases. The effect of polypharmacy was considered as an increased risk of exposure to hepatotoxic drugs and it would be interpreted as the role of only hepatotoxic drugs. Although the results of this study support this belief, there are some concerns about only considering hepatotoxic drugs as the cause. Initially, polypharmacy and liver disease were significantly associated despite an absence of exposure to hepatotoxic drugs. This raised the question about whether there would be room to explain this using polypharmacy during non-exposure to hepatotoxic drugs. This would cause multicollinearity because of the strong

correlation between exposure to hepatotoxic drugs and polypharmacy which makes the estimates less precise. Further studies are required to examine the exact role of polypharmacy on liver diseases, apart from hepatotoxic drugs.

This study has limitations. First, as mentioned earlier, the multicollinearity between polypharmacy and hepatotoxic drugs has remained. To get rid of it, one of the strongly correlated variables should be removed from the regression equation. However, the two variables—polypharmacy and exposure to hepatotoxic drugs—were most important for this study hypothesis. Additionally, the omission of relevant variables results in bias. Therefore, the two variables were retained which does not actually bias the results. Second, the hepatotoxic mechanisms for individual drugs and drug interactions were not considered due to the large number of drugs and participants. To consider these specific mechanisms and drug interactions, a small but focused study is required rather than a large population-based study. Besides, the information acquired from the claims data is insufficient for the pathological status. Although there are specific types of liver injuries linked to some causative drugs [112,135], most of the drugs could elevate liver enzymes and cause liver injury [43], and many of the liver diseases are coded with non-specific types of diseases in a practical setting.

However, it had implications that it is the first to examine the relationship between polypharmacy and liver disease and it also considered the role of exposure to hepatotoxic drug in this relationship.

Those two studies confirmed the associative risk of polypharmacy in the kidneys and liver among older adults using a large population data. Though further studies are required to provide evidence for the risk of polypharmacy, strategies for reducing it should be considered simultaneously for the next step in polypharmacy management.

In Korea, efforts have been made to propagate the rational use of medicines by the Korea Health Insurance Review and Assessment (HIRA). They undertook the policy of the Evaluation Project on Appropriate Prescribing (EPAP) in 2001. It includes indicators involving antibiotics for acute respiratory tract infections, overuse of injection, prescribing of specific medication group (NSAIDs, corticosteroids, etc.) as well as polypharmacy (the number of drugs prescribed together and number of prescriptions with 6 or more drugs). However, it has focused on institutions rather than patients because these policies were made to assist HIRA in reviewing and assessing prescription patterns and in providing feedback to institutions. Patient-centered strategies should also be established to optimize the rational use of medicines and reduce polypharmacy

and the risk to individual patients.

The critical components of polypharmacy management were identified as criteria for inappropriate prescribing and deprescribing in the previous review. Each screening tool has different approaches for medicines that are no longer beneficial to the patient and can potentially risk a patient—each has its own advantages and disadvantages. Thus, they are useful when used properly. However, they are rarely used in the practical setting in Korea which is one of the most self-sufficient environments for implementing such management.

Therefore, such tools should be used proactively and in accordance with the management stage of the healthcare system. First, the explicit tools are efficient in detecting and screening a person with polypharmacy and inappropriate medicines because it can be applied consistently to a large population with full medical information. Especially, in Korea where an electronic medical record system has already been developed. It is useful to use explicit criteria to detect inappropriate prescription with full medical information. Second, implicit tools are essential for reducing polypharmacy and eliminating inappropriate medicines from individual patients with the full consideration. It is practically difficult to conduct clinical judgements and deprescribing. However, there would be opportunities to review a patient's medication, identify polypharmacy, and conduct

deprescribing when a mandatory health examination is conducted by the NHIS at least biennially.

VI. Conclusion

In conclusion, this dissertation found that the exposure to polypharmacy was significantly associated with the risk of kidney and liver dysfunction among older Korean patients. The effect of polypharmacy is consistent for kidney dysfunction. However, for liver disease, most of the effects of polypharmacy were mediated by the exposure to hepatotoxic drugs. This dissertation broadened the range of evidence about why polypharmacy should be avoided. Moreover, it emphasized on the need for polypharmacy management and provided stage strategies appropriately.

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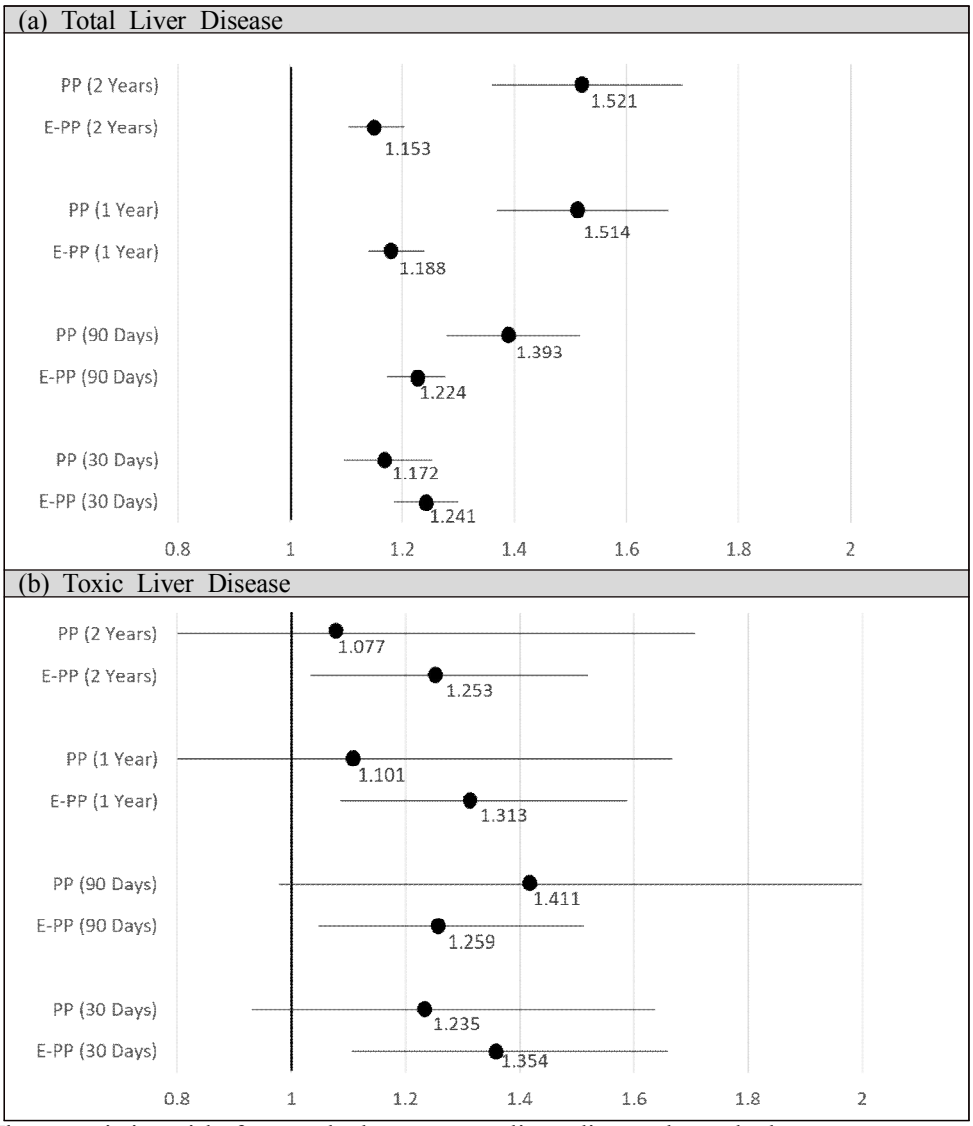
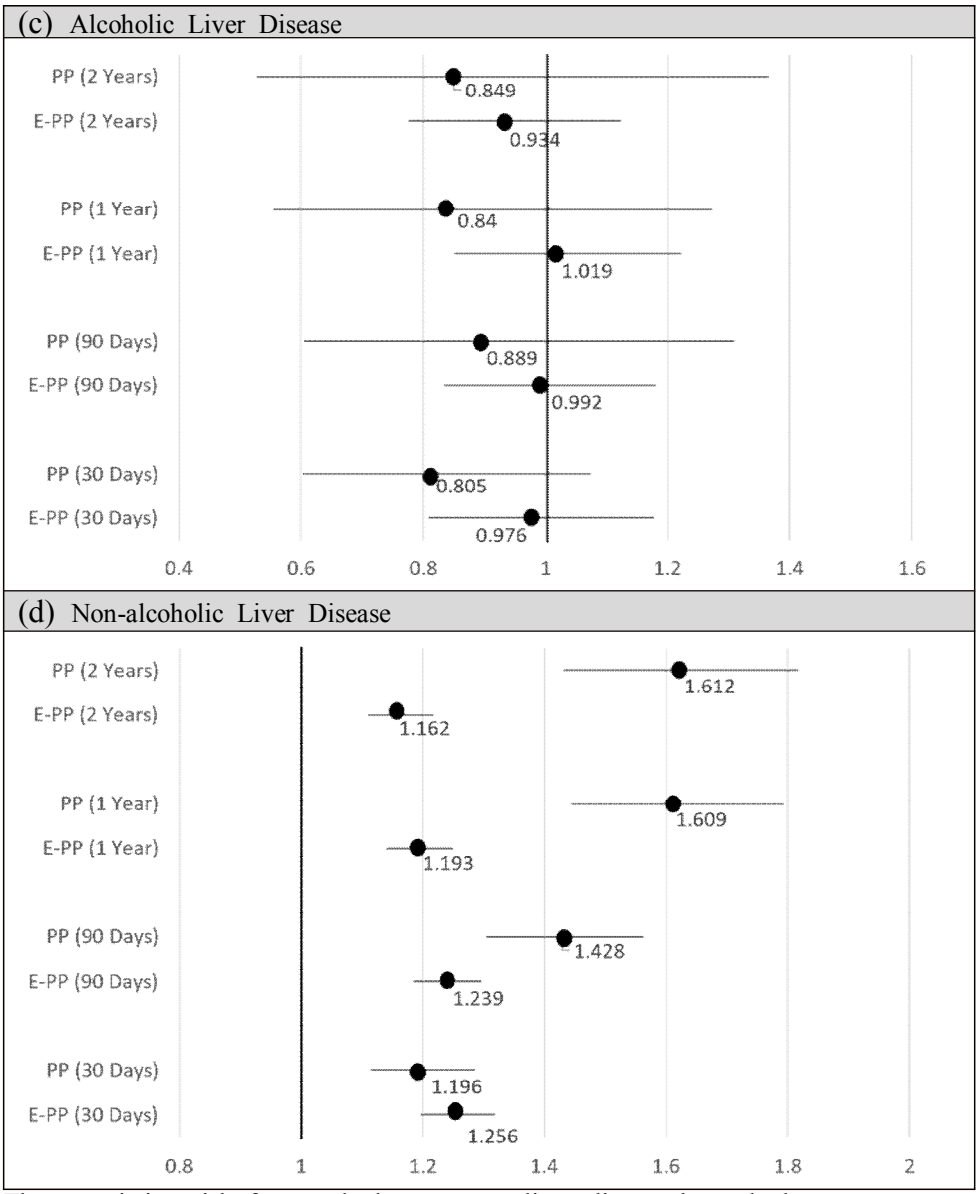
Appendix

Supplementary Figure S1.



The associative risk from polypharmacy on liver disease by polypharmacy exposure periods and specific types of liver disease: (A) In case of total liver disease, the association between polypharmacy and disease was significant across the different polypharmacy duration. In general, the odds with polypharmacy is higher than those with excessive polypharmacy except polypharmacy for 30 days. (B) In case of toxic liver disease, there was no significant association between polypharmacy and the disease, while the excessive polypharmacy was significantly associated with the risk of toxic liver disease regardless of polypharmacy exposure duration.

Supplementary Figure S1. (continued)



The associative risk from polypharmacy on liver disease by polypharmacy exposure periods and specific types of liver disease: (C) In case of alcoholic liver disease, there were no significant association between polypharmacy and the disease regardless of polypharmacy exposure duration and whether to polypharmacy or excessive polypharmacy. (D) In case of non-alcoholic liver disease, the association between polypharmacy and the disease was significant across the different polypharmacy duration. In general, the odds with polypharmacy is higher than those with excessive polypharmacy except polypharmacy for 30 days.

Supplementary Table S2.

Several types of Equations for estimating the GFR.
1) CKD-EPI equation $\mathrm{eGFR(ml/min/1.73}m^2\mathrm{)} = 141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018[if\ female] \times 1.159[if\ black]$ $\kappa = 0.7\ if\ female\ or\ 0.9\ if\ male;\ \alpha = -0.329\ if\ female\ or\ -0.411\ if\ male$ 2) MDRD Study equation $\mathrm{eGFR(ml/min/1.73}m^2\mathrm{)} = 186 \times Serum\ Creatinine^{-1.154} \times Age^{-0.203} \times [1.210\ if\ Black] \times [0.742\ if\ Female]$ 3) The Cockcroft-Gault equation $\mathrm{eC}_{cr}\mathrm{(ml/min)} \frac{= (140 - age) \times weight(in\ kilograms) \times [0.85\ if\ Female]}{72 \times creatinine(in\ mg/dL)}$

Supplementary Table S3.

Definition of Risk Factors for Kidney Dysfunction

Variable	Definition
Disease-specific	
HTN	Patients with diagnosis ICD10 code of 'I10', 'I11', 'I2', 'I13', 'I15'
DM	Patients with diagnosis ICD10 code of 'E10', 'E11', 'E12', 'E13', 'E14'
CHF	Patients with diagnosis ICD10 code of 'I50'
IHD	Patients with diagnosis ICD10 code of 'I20', 'I21', 'I22', 'I23', 'I24', 'I25'
Arrythmia	Patients with diagnosis ICD10 code of 'I49'
Gout	Patients with diagnosis ICD10 code M10
Obesity level (BMI)	underweight (less than 18.5); normal weight (18.5 to 22.9); overweight (23.0 to 24.9); obese I (25 to 29.9); and obese II (more than 30).
Hyper-TC	Patients with total cholesterol of 240 mg/dL or more
Hyper-TG	Patients with triglycerides of 150 mg/dL or more
Lower-HDL-C	Patients with HDL-C of 40mg/dL or less
Higher-LDL-C	Patients with LDL-C of 140mg/dL or more
Medication-specific	
ACEIs	Patients who had prescription of ACEI with a ratio of 50% or more of prescription days between prescription date and index date based on prescription history within 1 year.
ARBs	Patients who had prescription of ARB with a ratio of 50% or more of prescription days between prescription date and index date based on prescription history within 1 year.
Metformin	Patients who had prescription of Metformin with a ratio of 50% or more of prescription days between prescription date and index date based on prescription history within 1 year.
Statins	Patients who had prescription of Statin with a ratio of 50% or more of prescription days between prescription date and index date based on prescription history within 1 year.
NSAIDs	Patients who had prescription of NSAIDs with a ratio of 50% or more of prescription days between prescription date and index date based on prescription history within 3 months
PPIs	Patients who had prescription of PPIs with a ratio of 50% or more of prescription days between prescription date and index date based on prescription history within 3 months
Allopurinol	Patients who had prescription of Allopurinol 2 weeks before the index date.
Acetaminophen*	Patients who had prescription of PPIs with a ratio of 50% or more of prescription days between prescription date and index date based on prescription history within 3 months
Antibiotics*	Patients who had prescription of antibiotics 2 weeks before the index date.
Methotrexate (MTX) *	Patients who had prescription of MTX 2 weeks before the index date.
Calcineurin	Patients who had prescription of Calcineurin inhibitors 2 weeks before

inhibitors*	the index date.
Osmotic agents*	Patients who had prescription of Osmotic agents 2 weeks before the endoscopy date.
Contrasts*	Patients who had prescription of Contrasts 2 weeks before the endoscopy date.
Lifestyle-related	
Smoking	Based on the consecutive response from questionnaires, smoking status was distinguished: non-smokers(N-N), current smokers(N/Y-Y), and ex-smokers(Y-N).
Drinking status	Based on the number of drinking days per week, drinking status was categorized as non-drinker (0 to 1) and drinker (2 to 7).
Physical activity	Based on the number of exercise days per week for moderate physical activity for at least 30 minutes, physical activity status was classified as non-exerciser (0 to 1); exerciser (2 to 7).

HTN: hypertension; DM: diabetes mellitus; CHF: congestive heart failure; IHD: ischemic heart disease; BMI: Body Mass Index; TC: Total Cholesterol; TG: Triglycerides; HDL-C: High-Density Lipoprotein Cholesterol; LDL-C: Low-Density Lipoprotein Cholesterol;
ACEIs: Angiotensin-Converting-Enzyme Inhibitors; ARBs: Angiotensin II Receptor Blockers; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs; PPIs: Proton Pump Inhibitors
Antibiotics include vancomycin, penicillin, cephem, macrolide, amphenicol, fluoroquinolone, sulfonamides, fosfomycin etc
Variables with * were not included in the main analysis while basic statistical differences were described in Supplementary Table S6.

Supplementary Table S4.

Hepatotoxic drug list
Allopurinol; Amiodarone; Amlodipine; Amoxicillin; Amoxicillin/Clavulanic acid; Aspirin (acetylsalicylic acid); Atorvastatin; Azathioprine; Azithromycin; Bentazepam; Captopril; Carbamazepine; Cefuroxime; Chlorpromaxine; Ciprofloxacin; Clomethiazole; Clomipramine; Clopidogrel; Cloxacillin; Cotrimazole; Cyclophosphamide; Diclofenac; Disulfiram; Doxycycline; Duloxetine; Ebrotidine; Enalapril; Erythromycin; Ethinylestradiol/levonorgestrel; Fenofibrate; Flucloxacillin(floxacillin); Fluconazole; Flutamide; Fluvastin; Halothane; Ibuprofen; Interferon_beta_1a; Isoniazid; Isoniazid-Rifampicin; Lamotrigine; Leflunomide; Levofloxacin; Lisinopril; Lovastatin; Mercaptopurine; Minaserin; Minocycline; Naproxen; Nefazodone; Nimesulide; Nitrofurantoin; Norfloxacin; Omeprazole; Paracetamol (acetaminophen); Paracetamol and dextropropoxyphene; Paroxetine; Phenytoin; Piroxicam; Ranitidine; Rifampicin (rifampin); Rifampicin - isoniazid − pyrazinamide; Sertraline; Simvastatin; Sodium aurothiomalate Stanoozolol; Sulfasalazine; sulindac; telithromycin; terbinafine; tetrabamate; thiamazole; ticlopidine; trimethoprim; trovafloxacin; valproic acid; verapamil

Supplementary Table S5.

Basic statistics for matched variables before and after matching (Study 1)

	Unmatched					Matched				
	Case (n=14,657)		Control (n=67,257)		p	Matched Case (n=14,577)		Matched Control (n=14,577)		p
	Freq.	(%)	Freq.	(%)		Freq.	(%)	Freq.	(%)	
Gender										
Female	8282	56.51	36344	54.04	<.0001	8209	56.31	8209	56.31	1
Male	6375	43.49	30913	45.96		6368	43.69	6368	43.69	
Age (year)										
65≤ <75	10244	69.89	52998	78.80	<.0001	10237	70.23	10237	70.23	1
75≤ <85	4413	30.11	14259	21.20		4340	29.77	4340	29.77	
Coverage										
Health Insurance	14645	99.92	67221	99.95	0.1988	14577	100.00	14577	100.00	1
Medical Aids	12	0.08	36	0.05			0.00		0.00	
Income level[1]										
High	8380	57.17	39955	59.41	<.0001	8337	57.19	8448	57.95	0.405
Medium	2999	20.46	13660	20.31		2988	20.50	2950	20.24	
Low	3278	22.36	13642	20.28		3252	22.31	3179	21.81	
Residential area[2]										
Metrocity	5384	36.73	23061	34.29	<.0001	5373	36.86	5383	36.93	0.559
City	3293	22.47	14426	21.45		3287	22.55	3214	22.05	
Others	5980	40.80	29770	44.26		5917	40.59	5980	41.02	
Years of baseline examination										
2009	7300	49.81	15406	22.91	<.0001	7240	49.67	7240	49.67	1
2010	6113	41.71	44392	66		6100	41.85	6100	41.85	
2011	1198	8.17	7217	10.73		1194	8.19	1194	8.19	
2012	46	0.31	242	0.36		43	0.29	43	0.29	
Initial Kidney function										
eGFR ≥90	1051	7.17	11865	17.64	<.0001	1044	7.16	1044	7.16	1
eGFR ≥60	13606	92.83	55392	82.36		13533	92.84	13533	92.84	
Follow-up duration										
1≤ < 2	7482	51.05	32333	48.07	<.0001	7420	50.9	7420	50.9	1
2≤ ≤ 3	7175	48.95	34924	51.93		7157	49.1	7157	49.1	

[1]Income level is classified into the 10th quintile through the premium information imposed by the household unit in the health insurance, and the upper 3 quintiles are classified as High group; Medium group; And the lower 4 quartiles are defined as low group.
[2]Residential area is classified into the three groups considering administrative region and city population size: Metrocity (Seoul and Gyeonggi-do); City (Busan, Daegu, Incheon, Gwangju, Daejeon, Ulsan); and Others (Other region)

Supplementary Table S6.

Basic statistics for matched variables before and after matching (Study 2)

VARIABLES		CASE		CONTROL		P-value
		Freq.	Percent	Freq.	Percent	
Matched variables						
Gender	Male	12,173	45.72	12,173	45.72	1
	Female	14,450	54.28	14,450	54.28	
Age	65 ~ 74	18,570	69.75	18,570	69.75	1
	75 ~ 84	7,711	28.96	7,711	28.96	
	85 ~	342	1.28	342	1.28	
Income level	High	15,909	59.76	15,875	59.63	0.95
	Medium	5,492	20.63	5,549	20.84	
	Low	5,222	19.61	5,199	19.53	
Coverage type	Health Insurance	26,519	99.61	26,529	99.65	0.48
	Medical Aid	104	0.39	94	0.35	
Region	Metropolitan	9,158	34.40	9,124	34.27	0.84
	City	5,934	22.29	5,991	22.50	
	Others	11,531	43.31	11,508	43.23	
Non-matched variables						
Health condition (CCI)	Normal	17,611	66.15	19,061	71.60	<.0001
	Mild	8,168	30.68	6,733	25.29	
	Severe	844	3.17	829	3.11	
Hypertension		15,906	59.75	15,151	56.91	<.0001
Diabetes		7,023	26.38	6,022	22.62	<.0001
Hyper Total Cholesterol		3,866	14.52	3,570	13.41	0.00
Obesity	Underweight	969	3.64	1,317	4.95	<.0001
	Normal weight	9,273	34.83	10,149	38.12	
	Overweight	6,940	26.07	6,610	24.83	
	Obese	9,441	35.46	8,547	32.10	
Abnormal Liver function	AST	2,860	10.74	1,330	5.00	<.0001
	ALT	2,842	10.67	1,239	4.65	<.0001
	Gamma GTP	4,769	17.91	2,688	10.10	<.0001
Drink Habit	Never	20,793	78.10	22,170	83.27	<.0001
	Moderate	2,701	10.15	2,128	7.99	
	Severe	3,129	11.75	2,325	8.73	
Interested variable						
Polypharmacy	N-PP	19,798	74.36	20,759	77.97	<.0001
	PP	5,854	21.99	5,187	19.48	
	E-PP	971	3.65	677	2.54	
Exposure to hepatotoxic drugs		5,400	20.28	3,333	12.52	<.0001

Supplementary Table S7.

Exposure to other medicines related with kidney function

	Matched Case (n=14,577)		Matched Control (n=14,577)		p-value
	Freq.	(%)	Freq.	(%)	
Other medicines related with Kidney function					
Osmotic agenton	263	1.80	306	2.10	0.07
Contrast	7	0.05	20	0.14	0.01
Calcineurin inhibitor*	3	0.02	0	0	0.25
Methotrexate	0	0	0	0	1
Fosfomycin*	0	0	1	0	1
Sulfa	25	0.17	14	0.10	0.08
Penicillin	531	3.64	533	3.66	0.95

국문 초록

다약제복용(Polypharmacy)은 다수의 약물을 동시적으로 복용하는 것으로, 다수의 질환을 이환하는 노인에서 노출될 가능성이 높다. 또한 노인의 경우 연령 증가에 따른 생리학적 변화로 약물-약물 상호작용, 약물 부작용의 위험 역시 증가할 수 있어 주의가 필요하다. 다약제복용으로 인한 부정적인 건강결과로 주로 사망, 낙상과 골절 등에 대한 영향을 확인해왔으며, 약물을 대사하고 배출하는 간과 신장에 대한 영향을 분석한 연구는 부족하다. 따라서 본 연구는 노인에서의 다약제복용이 신기능 및 간 질환의 위험에 대해 미치는 영향을 확인하고자 하였다.

건강보험 노인코호트(NHIS-The Senior Cohort, 2002-2013)를 이용하여 Nested Case-Control Study를 각각 수행하였다. 다약제복용은 일년동안 일일 평균 5개 이상 약물을 복용하는 경우로 정의(PP: 5개 이상 ~ 10개 미만; E-PP: 10개 이상)하였으며, 경구제제만을 포함하였고, 성분별로 약물의 수를 구분하여 적용하였다. 신기능 저하는 eGFR 60 ml/min/1.73m^2 미만이고, 기저 상태 대비 10% 감소가 발생한 경우로 정의하였으며, 간 질환은 상병코드(K70, K71, K73-76)을 가진 경우로 정의하였다. 각 Case에 대한 정의에 대해서는 민감도 분석/하위개념 분석을 수행하였다. Matched case와 control을 구성하여 위험관련성을 확인하는 데에는 Conditional logistic regression를 이용하여 분석하였다.

다약제복용은 신기능 저하와 관련된 질환, 생활습관, 약물 등 여러 위험요인을 보정한 이후에도, 신기능 저하에 유의한 영향을 미치는 것으로 확인되었다(PP: aOR, 1.21; 95% CI, 1.14 - 1.29; E-PP: aOR,

1.46; 95% CI, 1.30 – 1.64). 또한 신기능 저하 정의를 달리한 분석에서도 다약제복용과 신기능 저하의 관련성은 유의하게 나타났다.

다약제복용은 간 독성 약물 노출 외 여러 위험 요인 및 교호작용을 보정한 후에도 간 질환의 위험에 유의한 영향을 미치는 것을 확인하였다 (Total Effect: aOR=1.06, 95% CI=1.03−1.08). 하지만, 많은 부분이 간 독성 약물 노출에 의해 매개되는 효과로 확인되었다. 그 외 간 질환의 하위개념 분석에서는 독성 간질환과 알코올성 간 질환에서는 다약제복용의 효과를 확인할 수 없었으며, 비알콜성 간 질환에 대해서는 다약제복용의 유의한 효과가 확인되었다.

본 연구는 처방 의약품 정보와 건강검진 및 의료이용 정보를 모두 연계된 빅데이터를 분석한 연구로, 동시에 많은 약물의 사용이 약물의 대사 및 배설에 중요한 간과 신장에 대해 유의한 영향이 있음을 확인한 연구로서 의미가 있다. 이는 다약제복용에 대한 정책적 개입의 필요성의 근거가 되며, 다약제복용 관리를 위한 환자 중심적 접근 방안의 중요성을 제시한다.

주요어: 다약제복용, 노인, 신기능, 간질환
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